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AMERICAN SURGICAL ASSOCIATION
AT CHICAGO, ILL.
MAY 3rd and 4th, 1944

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TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT CHICAGO, ILL.

MAY 3-4, 1944

ADDRESS OF THE PRESIDENT

THE STATE OF THE ASSOCIATION

FREDERICK A. COLLER, M.D.

ANN ARBOR, MICH.

THE AMERICAN SURGICAL ASSOCIATION is sixty-five years old today. At no time in its distinguished and illustrious annals have we its members been confronted with so many issues basic to the future of our profession and to our field of specialization. It is, therefore, with more than usual humility that I seek for words with which to thank you for giving to me for this brief moment the ultimate honor in American Surgery, and to signify my sense of lacking those qualities so needed in times of change, urgency and crisis.

For two years and a half our nation, with its allies, has been engaged in war, a struggle to the death against barbaric and brutal forces of darkness. The ferocity and enormity of it have torn deeply into the structure of civilization and into our lives, and have destroyed most of our peace time plans and visions. Every member of our Association has taken a part either in the planning on the home front or in active prosecution of the conflict in the Armed Forces, to the limit of his strength and ability. The time is not yet when we can summarize and evaluate these efforts, but let us express now our admiration and appreciation of the many from the Association and from our profession who have been and are now so ably and unselfishly carrying on the high purpose of medicine on active service with our Armed Forces over all seas and on all lands.

I am sure we have all wondered at times in the past year what more we should be doing to maintain the standards for which we have long struggled

* Delivered before the American Surgical Association, May 3, 1944, Chicago, Ill.

and how best we might direct our activities to keep abreast of, and if possible to lead, the changes that are taking place in the shifting relations of medicine to our social structure. Since these changes carry an implied challenge to our past performance and veil the future with uncertainties it has seemed to make it important to bring before you now some of the issues that present themselves to us as individuals and as members of the Association, therefore, I shall limit myself to a simple recital of those that seem most pertinent to Surgery at this time. Of necessity, I must repeat many of the points emphasized in the Presidential addresses of my recent predecessors, notably those of Arthur Dean Bevan, Dallas Phemister, Vernon David and Evarts Graham in his reincarnation of Founder Gross. The purpose of the Association is in general known to all of us, but lest we forget let me repeat from the Constitution: "The object of this Asssociation shall be the cultivation and improvement of the science and art of surgery, the elevation of the medical profession and such other matters as may come legitimately within its sphere." This is the broad view, one that we have at times forgotten and represents a goal toward which we should constantly reorient ourselves.

RELATIONS TO THE SOCIAL STRUCTURE

The relations of the medical profession to the social structure of our country have been under discussion for years, the threat of change becoming more and more acute. Whether the free competitive type of practice under which we have grown up shall in part or wholly be replaced by a controlled and subsidized method of caring for the sick is a possibility that confronts us. Many forms of cooperative practice have been suggested and there seems little doubt but that the profound social and economic conditions that will follow the war will result in significant and perhaps revolutionary changes in medical practice. It is not timely to elaborate here upon plans for future medical care, but one may state that thus far in the face of threatened change, the leaders of medicine have spoken at times in muted voice and in feeble tone. We can only hope that medicine will provide statesmen of sufficient stature to direct these movements into the high levels toward which we have striven during the time when medicine was under the dominance of the individual. As an association, perhaps we do not wish to attempt participation in such leadership, but whether we wish it or not we have a duty and an important interest in safeguarding our ideals of surgical practice if there come changes in the established methods of caring for those who are ill. At present there are forces working to remould Medicine through the more or less violent actions and reactions of pressure groups. The future health of the nation is worthy of greater consideration and if ever it be managed with an appreciation of its worth, it would demand a Minister of Health in the Cabinet with competent advisors from the laity and the profession who together could work out in an orderly fashion a plan that would be for the betterment of all. A statesman has said: "The health of the people is the first concern of government"; and we can

rightly insist that it be given statesmanlike consideration rather than that it be determined by political expediency.

RELATION TO MEDICAL EDUCATION

Under the stern necessity of war there have come almost unbelievable changes in medical education the pattern of which has been so slowly and painfully developed in the past thirty years. The selection of students for entrance to Medicine is now in part in the hands of the representatives of the Army and the Navy. Premedical training is shortened and its content changed, while the medical course itself is accelerated to a continuous performance. We are all heartily agreed with these or with any courses that will win the war and safeguard the health of our fighting men but we must realize that these changes are those of expediency and that they will give birth to vexing problems in the future. A study of medical education at this time discloses a self-confessed deterioration of instruction in many schools with the possibility of a serious breakdown in most, if there occur further depletion of faculties, lowering of educational requirements, or a let-down in the personnel qualifications of trainees assigned to medical schools. Graduate Training worthy of the name has ceased. The present 9–9–9 program is a distinct aid in caring for sick and injured civilians, but contributes little to what we have come to consider true Graduate Education. In the endeavor to spread the intern crop as widely as possible to help out the home front, many men are forced to accept internships in hospitals where training is virtually absent or present only in what might be described as a trace in preparation for their career in the Army and the Navy. This means that after the war there will be from 20,000 to 30,000 young men who will have had educational opportunities of a character inferior to those offered in the prewar period.

It is true that in many instances the training and experiences gained in Service will compensate in part or wholly for these deficiencies. There is no doubt but that the discipline, necessity for independent decision and habit of cooperative action acquired on active service, develop many admirable traits better than do any other school. However, many of these young men will demand further training of the orthodox variety after hostilities cease.

This task falls directly on the shoulders of those of us who have remained at home and the manner in which we carry it out will importantly determine the character of surgical service rendered to this country for the next generation. There has been set up from our profession a committee for Post-War Planning for Medical Services with representatives from the American Medical Association, the American College of Surgeons, and the American College of Physicians and the Army, Navy, Public Health Service and the Veterans Facility which is working to prepare to fill the needs and wishes of the demobilized medical officers. In order to get some idea of what the medical officers now in Service will want after demobilization, a ques-

tionnaire will be sent to every medical reserve officer on active duty. It is hoped that these returns will clarify to some extent the problems that face us. A subcommittee is now active in studying the question of providing Graduate Training in the medical and surgical specialties for those whose training has been interrupted or never started because of service with our Armed Forces. Feeling that the members of this Association should have the opportunity and would have the will to direct these efforts to enlarge and improve schemes for advanced training in surgery and its specialties, a committee was appointed in November with the sanction of your Council, to explore the field and to seek advice and help from every member of the Association. This committee will work with the main committee for Post-War Planning and carry your thoughts and aid to it. While no one can predict with accuracy what the needs of the future will be, we can plan to meet certain demands that inevitably will be made on our clinics, hospitals and schools. Judging from personal correspondence with men on Active Service, their desires for further training in Surgery will cause them to fall into several well defined categories.

First: Many well trained men will want refresher courses designed to refamiliarize them with those phases of civil surgery not seen in military experience. The demand will be not only on the clinic but also on the laboratories of the basic medical sciences.

Second: A larger group will comprise those men who have had an internship or a short residency who will seek training that will prepare them to take the Specialty Board Examination. This offers many delicate and difficult problems to us and to the Boards. By and large, the Boards will give credit for one year spent in military service with credit beyond that time given only after a careful evaluation of work actually done. We must provide opportunity not only for those whose training has been held up by the war but we have a duty as well to the on-coming medical graduates, and those worthy of advanced training in both classes should receive it. In order to accomplish this objective we will have to increase the number of available residencies, by increasing the number of hospitals where such training is available and by temporarily at least enlarging the number of residencies in those hospitals where acceptable training is now offered. The American College of Surgeons is committed to a greatly enhanced effort to stimulate and aid hospitals in setting up new schools of Graduate Training and there is no doubt but that the number of hospitals giving adequate training will be materially increased. In the past, there has been the greatest divergence in the methods used in carrying on advanced training in the hospitals of this country. Most frequently it has been effected by precept, in the ward and the operating room. Its greatest weakness has been in the lack of a proper integration of the clinical and basic medical sciences. A rescrutiny of our methods of training with the addition to it of more opportunities for study of anatomy, pathology, physiology and chemistry in relation to clinical problems would enable us to offer our residents better training at more

truly university levels and would enlarge the number of those to whom such training could be offered. In short, the stimulus of meeting the challenge of this emergency may well be the opportunity to reorganize and improve the quality of our Graduate Teaching.

In the past the opportunities for Graduate Training have been offered to a carefully selected group and many of the men who now will want advanced training would not have qualified for it in the ordinary course of events. It is natural that one will be influenced in choosing a resident by a man's Service record, but this alone is not enough; in addition he must be competent and intellectually worthy of this training. I do not know how best to select men from this great group for Fellowship and residencies, except that each of us will instinctively use the old yardsticks that we have found satisfactory in the past; and we should not be satisfied with short measure since, after all, our responsibility is to the American people of the future as well as to aspirants of today.

Residencies and Fellowships require money, and while the government may offer financial support to veterans for vocational training, we would be well advised also to plan to meet these needs from other sources. Residents are essential to the proper functioning of a hospital, yet, in the past hospitals have been willing to pay everyone on the staff except the physicians in training. There is every reason why hospitals should support residents who not only improve the care of the patient but make up their staff in the future. We should not only seek for funds with which to carry additional residents but we should increase their stipend to a level of financial decency. Hospitals, Medical Schools, Foundations, private individuals all should be approached for the money to carry forward this training program so vital to the health of the nation for the next two decades. If every member of this Association, who is not in the Armed Forces supported a Fellowship for three years, it would be a minor financial burden to us and would give training to 200 men. If we put our minds to it, the financial difficulties could largely be settled within the resources of our own communities.

A *third* group, a much smaller one, should be borne in mind, that is, those men qualified to do and desirous of carrying on research. We should have laboratories and financial support ready for them on their return. It is imperative that opportunities for investigation be given every young man who wishes to do research, as after this war the torch of science will still be burning in only a few spots on the earth. After the war only Russia and Great Britain, of the great European nations, will be able to foster scientific investigations and they will be carrying in addition a tremendous load in reconstruction and readjustment. Following the destruction caused by years of heroic and bitter war, China will be obliged to start her schools from scratch and will look to us for aid in training those who will care for the health of her enormous population and rebuild and develop her medical centers. South America will want even closer intellectual association with our schools and clinics, in the face of the weakness or absence of the

European medical centers with which they formerly were associated. The thought of these responsibilities is a staggering one, but if dwelled upon will serve to bring home to us the importance of planning and preparation for post-war graduate study and research not only for our own but for a large part of the world.

SPECIALISM

We as an Association are vitally interested in every phase of surgical evolution. Since our organization in 1880, there have been many changes in surgical practice brought about by the rapid development of knowledge and technics. The increase of specialism has more than kept pace with the speed of our intellectual art itself but its earlier manifestations were sporadic and without continuity. It was not until surgery itself began to advance after the conquest of pain and sepsis in 1846 and 1867 that specialization, as we know it today, had its origin. The founder of our Association, Samuel D. Gross, stated in 1876 that: "It is safe to say that there is not a medical man on this continent who devotes himself exclusively to the practice of surgery and that American medical men are general practitioners and cover the entire field of medicine, surgery and obstetrics." At the present time approximately 50,000 men in the United States specialize and at least 25,000 limit themselves to practice in some one field. There are now twelve special departments of surgery, all of them except obstetrics and gynecology have had their origin in what we call general surgery. These surgical specialties were originally created by general surgeons who because of opportunity or interest devoted their main efforts to one phase of their art. True specialization is a striving for perfection and we owe a great debt to those who have by their efforts in limited fields so greatly enhanced our knowledge of the whole. At the time when our system of medical education was so radically reorganized and put on its present basis, commercial specialism based solely on a desire for income, and justified by a two weeks course in Vienna, was a threat to honest specialization, a menace to the public, and a shame to our profession. In the time that has passed since then, through our own efforts, expanded through the Colleges and Boards, we have put the requirements for specialization on a high plane. Granting that special study and perfection of technics in a chosen field have increased our knowledge and skill, the establishment of rigid lines of separation from the parent stem offers dangers for the future. To quote Victor Bonney: "Whereas before their advent, the surgeon made the specialty, it is now possible for the specialty to make the surgeon." A specialty justifies itself only so long as it advances the border lines of knowledge in its field, because of intensive application to it or because it develops the technic peculiar to that field to a high degree. To carry on a specialty on the latter grounds is a convenience to the surgeon and may benefit the patient; but as a basis for training succeeding generations it presents many dangers since technics may become dominant while the fundamentals of surgery are neglected. When

a specialty becomes static and the aspirant in that field is trained solely in the specialty, he will tend to become a mere technician, with a limited usefulness and a narrow vision. If the process continues, his successors trained by him, in turn, will fall heir to progressive limitations. We will all agree that better surgical work is done in any field if one concentrates one's efforts on that objective, on condition that one is well founded and informed on surgery as a whole. Specialization is necessary and desirable but only if it continues along the broad path in which it had its origin. As a matter of fact we all are specialists, since each of us has his own particular field of talent. These aptitudes are developed by our own interest or forced upon us by chance, opportunity, or by some paper or book we have written. I often wonder, what is a general surgeon? The most one can say is that those of us who call ourselves general surgeons take pride in believing that we look upon the body as a whole and exhibit an interest in studying its responses to abnormal conditions of disease. In addition we may be known for our dexterity in thyroidectomy, colectomy, gastrectomy or pneumonectomy. These are our specialties, and of course many men who call themselves specialists would, under this concept, qualify as general surgeons. But if we all indulge in specialism to some degree, we all must admit the necessity of a broad training in the fundamentals before limiting our efforts to one phase of the art. What we should strive for is not to make everyone a general surgeon, but to make all who practice in any surgical field, Generals in Surgery. The thoughtful men in all fields of surgical endeavor admit the necessity of close integration and cohesion between fundamental and special training. One year ago Vernon David brought this matter to your attention and appointed a committee to explore the possibilities of a basic examination in Surgery for all aspirants to surgical practice of any type. In General Medicine, such a basic examination in the broad principles of medicine is given, and is a requirement for the candidate before he can seek certification as a specialist. Unfortunately in Surgery, there has not been the same coordinated development of standards for certification due in some part to the long past reluctance of members of this association, either to recognize the need for standards or to aid in their establishment. Consequently, standardization of surgical practice in this country has developed from many roots. The American College of Surgeons was formed in 1912, and first setup requirements for admission to Fellowship. At that time graduate training in surgery and its specialties was practically nonexistent except through the apprentice system. The task of passing upon the capability of those doing surgery in a great nation, in places varying in size from cities with millions to villages with but hundreds, was a difficult one and impossible of accurate achievement. One cannot, however, overestimate the importance of the event although this is often overlooked by those who criticize the College for accepting Fellows who were deemed unworthy. The difficulty lay in a complete absence of accurate yardsticks of excellence and in the struggle to reconcile practice in city and in country. The American College of Surgeons not only attempted

to designate the skillful in practice, but it improved the tools with which the surgeon worked. Through the standardization of hospitals, it provided the surgeon with an environment in which he could have every facility and in which the well-being of the patient was safeguarded. Through its committee on Graduate Training, it has aided hospitals in developing facilities for advanced education and has consistently urged that these facilities move toward higher educational levels. As time went by, standards for educational requirements for admission to Fellowship were raised slowly, but one may prophesy surely, in the attempt to include and reconcile the different types of practice in town and city.

In the meantime the Surgical Boards were organized, by which higher standards were set. The Board of Ophthalmology was organized in 1916. Later there came Boards in Otolaryngology, Obstetrics and Gynecology, Dermatology and Syphilology, and, in 1933, the American Medical Association authorized the Council of Medical Education and Hospitals to formulate standards of administration for Boards to be based upon the form of those already established. There are now fifteen Boards, nine of which are related in some degree to Surgery. The American Board of Surgery organized at the initiative of this Association came into active being in 1937 and has had an outstanding record of influence and stimulation. Thus through a series of historical accidents, one may become certified as a surgeon by passing through any one of the nine portals of the Boards or under the arch of the College. We cannot turn back the clock and we must admit that both the Boards and the College fulfill important functions and should be given our cordial support. It is regrettable that so many ways of reaching the heights have been hewn but in the last analysis this redundancy of effort has been due to the rapid development of surgery and its specialties and to the pride of the specialist in making his own path to his own particular field. One may well ask, would it not be to the best interests of surgery to coordinate and amalgamate in some way the standards of that Art? All of the Boards require a knowledge of the Basic Sciences in relation to health and disease, and everyone will admit that this knowledge is fundamental to everyone worthy of the title Surgeon no matter what his specialty may be. Could not there be developed a basic examination in surgical fundamentals that would be taken by all those wishing to become candidates for the Boards and for Fellowship in the American College of Surgeons? Passing such an examination would be a preliminary to later taking the Final Examination of the Specialty Boards and would admit the successful candidate to Junior Membership in the American College of Surgeons. Such a system would anchor firmly the specialists in the parent Art and Science and would bring together the various now divergent agencies that have a common cause, that is, the advancement of Surgical Practice and Service. These ideas have been discussed by the members of your committee and will be reported to you through the Chairman, Doctor Whipple. Meetings have been held with a similar committee from the American College

of Surgeons, Board of Orthopedic Surgery and the American Board of Surgery. It is hoped that some progress has been made in bringing about a cohesion in surgery that, if finally effected, will restore us to a state so that we may strive together towards a common goal. All of us must study this possibility and if, finally, it is deemed advantageous action may come.

Tradition and custom have decreed that the American Surgical Association shall remain a comparatively small organization but they likewise insist that we constitute a Forum in which the new advances in Surgery shall be presented each year. It is a question whether the two are longer compatible. You are familiar with the facts concerning our development, as they have frequently been presented to you. The year the Association was formed, the membership was set at 150, and the population of the country was 50 million. At that time, there were few specialists and it was a rarity for anyone to limit his work to surgery. In 1939 the membership was raised to 175 and the active membership has been increased slightly by lowering the retiring age to Senior Membership, and young men, not members of the Association, have been allowed the privilege of presenting papers if they are sponsored by a member. These changes have been helpful but they have not adequately solved the difficulties. We have admitted the necessity of having as members those in Surgical Specialties who are adding knowledge and conducting research in their chosen fields. We value the membership of these men and our programs have gained in breadth and interest by their contributions, but there is reason to believe that we would profit by a still wider representation of leaders in the specialties in our membership.

In considering the size and sphere of activity of the Association, we have apparently neglected to take into account our greatest contribution. Graduate Training in Surgery is largely a development since 1920 and has done more to stimulate original scientific work in surgery in this country than has any other force. A large part of the advance in surgery in the past 20 years has been due to the efforts of these young men in our laboratories and clinics, and a familiarity with surgical literature or an acquaintanceship with the younger group as they have come up for examination by Surgical Boards; impresses one with their superlative ability and their potentialities for leadership. Certainly everyone who passes a Surgery Board is not automatically a candidate for membership in the Association, but we must recognize the fruit of our Graduate Training Program and realize that never before in our history have we had so many capable young men engaged in forwarding surgical knowledge from whom we could profitably select new members. We should learn of their work at first hand and if we do not give them opportunity here they will develop societies of their own and leadership will drift from us. Most of them are now engaged in caring for the wounded, but many of them are worthy of our consideration and we should look forward to their incorporation into the Association when they return. If the Association is to maintain its proud place and live up

to its original tenets, we must recognize the almost unbelievable changes that have taken place in the personnel of our ranks due to our own efforts at bringing training in Surgery to higher educational levels. The population of the country is now nearly trebled since the initiation of our organization, approximately 20,000 men in this country limit their work to general surgery alone. Our American Board of Surgery has certified 3000 men and other Surgical Boards have certified more than this number. Surely to get the best from these, we could well consider some enlargement of our membership. During the next few years there will be available only a comparatively few vacancies for membership due to the passage of a like number of our members of the 60 mark. As we stand now, only one other force may increase this number, but let us hope it will operate feebly, or not at all.

Whether our membership is inclusive enough to represent major surgical progress in teaching, research and in the clinic, we can leave for the moment. Do we now give opportunity to all of our members who wish to present their work and ideas? Ever since I have been a member there have been many papers read by title, often the number thus offered has been nearly as large as those read on the floor. While we admit the difficulties and sincerity of the hard working program committee, many of our members have been piqued at having a paper over which they have slaved, thus presented by a sentence. At times resentment has been felt by those who did not get on the program and the apprehension of being passed by has often acted as a deterrent to further efforts. If this feeling could be removed, it is more than likely that the number of papers submitted would immediately be doubled. It would indeed be the rare paper submitted by any one of our members that would not be worthy of the audience.

In order to give opportunity for presentation of a larger number of papers, some adjustment of present practice would be necessary. The first meetings of the Association were held for three days, in fact our By-Laws read that: "The meeting shall continue for three days, unless otherwise ordered by a majority vote." Some time in the historical past the meetings dwindled by half a day and this year, as a war measure, perhaps with the fear that there would not be material enough to run the course, it was reduced to two days. Suggestions have been made many times that we could increase the number of papers read by allowing ten minutes for their reading. The possibility of having sections running simultaneously on papers of like interest has also been mentioned. Under our present system, discussion is often more limited than is the demand for it. Certainly every effort should be made to stimulate our members to present their work and to make each one feel clearly that his productions are solicited and welcomed. This problem of enlarging the program is one for study and I hope that the appointment of a committee will be authorized to make such recommendation as will enable an enlarged and more completely representative program to be offered at our future meetings.

The question of enlarging the membership in the Association is one that

has been much debated and one that is answered in divergent manner by our members. There must be a membership that would represent our maximal efficiency to carry out the avowed aims of the Association. This problem has been the subject of study and might profitably become so again because of the accelerated tempo of scientific progress. In the meantime, confronted as we are with so few vacancies in our ranks and with the many brilliant young men in all fields of surgical activity who could add to our prestige, might we not consider again the advisability of a modest enlargement now. It is five years since the membership was increased by 25. This increase has been well digested. I suggest that, in addition to filling the vacancies that occur each year we add for the next five years five men each year. This would increase our active membership to 200 in that time, certainly not a number larger than would contain the outstanding contributors to surgery in this country and Canada. I believe that without some increase at this time we cannot remain truly representative and that this enlargement will greatly strengthen the Association. If the problem is studied, as it should be and further changes seem advisable, they can be readily effected at any time by a vote of this body.

In conclusion, I would like again to pay tribute to the members of our Association and to the thousands of young men who are caring for the sick and wounded on the battle front. They have earned our deepest gratitude and their work merits our highest admiration. We read with pride the reports that come from the Surgeon-Generals of the Army and Navy in which are emphasized the vast improvement in the surgical care of our injured soldiers and sailors over those of previous wars. The public press ascribes this great advance as due to some product of laboratory ingenuity, such as plasma, sulfa, and penicillin. These are mere adjuvants that will eventually be replaced by better things, but the public likes to glorify the gadget.

The truth is that the health of our Armed Forces and those of our allies is being guarded by the best trained, most capable medical officers ever to serve with any armies in the history of war. They are giving a vital and vivid demonstration of the worth of the methods of teaching and training developed since the last war. The modern miracles of medicine and surgery are due to the men who perform them not to any minutiae of their technics. For their skill and devotion we acclaim them, taking pride in the fact that in some part at least, we have set the goal that they have reached. The future of Medicine and Surgery will be brilliant in their hands, in the present it is our task to prepare the way for their home-coming in such fashion that standards of training and achievement will be maintained and that the American Surgical Association will continue to hold the high part in Surgical leadership it long since assumed in the past.

Described by Brigadier General Rankin as "one of the finest dissertations on management of wounds which has been submitted through the Office of the Surgeon General of the U. S. Army," this paper by Colonel Churchill, arrived just as we were closing the first issue of the ANNALS OF SURGERY *devoted to the transactions of the American Surgical Association. It was immediately accepted to appear in the Annals with the Transactions as a contribution by Col. Churchill,* in absentia. *The Editors join the Association in welcoming this fine report from an important battle area, and in congratulating Col. Churchill for his high accomplishment in the field and in reporting such excellent work.*

THE SURGICAL MANAGEMENT OF THE WOUNDED IN THE MEDITERRANEAN THEATER AT THE TIME OF THE FALL OF ROME

COLONEL EDWARD D. CHURCHILL, M. C., A. U. S.

"I would remind you again how large and various was the experience of the battlefield, and how fertile the blood of warriors in rearing good surgeons."

T. CLIFFORD ALLBUTT.

FOREWORD

BY

BRIG. GEN'L FRED W. RANKIN, M.C.

DIRECTOR, SURGERY DIVISION, U. S. ARMY

The present-day health standards of our troops and survival rate among our wounded have been unequalled in the history of warfare. Perhaps one of the most important factors contributing to this highly gratifying record has been the role played by the professional consultants whose functions may be broadly described as administrative, correlative, advisory, educational and analytical. Consultants in the major fields of endeavor have been attached to every Service Command in the Zone of Interior and to all active Theaters of Operations. Selected on the basis of their special training and extensive background and on their eminent qualifications, they have been able to perform an incalculably valuable function in promoting higher standards of medical practice in this war.

As Surgical Consultant to the North African and Mediterranean Theater of Operations and representative of this group, Colonel Churchill has done more than improve the quality of surgery performed in this Theater. Uniquely equipped to perform his mission and imbued with the true scientific spirit, he early recognized the inadequacy of certain preformed concepts in the surgical management of the wounded. With this flexibility of mind and with an elastic organization, he has utilized an investigative approach and drawn

upon battlefield experience to evolve more rational and effective methods in the surgical care of the wounded. In this article, he has epitomized these observations and principles which constitute not only a contribution to war surgery but also to the advancement of medical science.

WOUND MANAGEMENT may be divided into three phases—initial, reparative and reconstructive. The first two are concerns of an overseas theater. The latter is the mission of the Zone of the Interior.

INITIAL SURGERY

The initial surgery of the forward area is primarily directed toward the preservation of life and limb. The immediate physiologic disturbances incident to blood loss and the wound itself are corrected by both resuscitative and surgical measures. Wound infection is prevented or controlled by surgery and chemotherapy.

Resuscitation from shock has two goals: first, to render the casualty transportable and preserve his life until a hospital can be reached; and second, to prepare the casualty to withstand life saving surgical procedures. Shock as observed in the forward area is caused by whole blood loss except in burns, crushing injuries or rapidly advancing infection. Plasma is used in the divisional area to prepare the wounded for transportation and keep them alive until they can reach a hospital. Whole blood would be preferable, but it is not practical to use transfusions within the divisional area.

Plasma alone is not adequate to prepare a seriously wounded casualty to withstand the surgical procedures that are essential, or to carry him through the critical postoperative period. After admission to hospital a limited amount is used to augment the effects of whole blood transfusion. Plasma is a substitute for whole blood only in the sense that it can be packaged and stored in adequate quantity in areas where blood cannot be obtained. Plasma is not a substitute for whole blood in the physiologic sense. For these reasons a Blood Transfusion Unit procures and processes whole blood in the base and distributes it to the Army installations.

Shipments of blood were made by L.S.T. to the Anzio beachhead in February. As the front advanced and forward landing strips were opened, blood has been shipped each day by plane. In approximately four months, over 16,000 pints of whole blood have been drawn and processed for delivery to the Fifth Army. The blood is drawn by vacuum into bottles that are used only once. Glucose is added to the citrate as a preservative. Each flask of blood is triply checked for type, examined by smear for malaria and Kahn-tested.

Although Type "O" blood is commonly referred to as "universal donor" blood, its use in large amounts in patients of other types is hazardous unless the agglutinin titer is low. Every bottle of blood is titered and only those with an agglutinin titer less than 1 to 64 are issued as "universal donor" blood. All banked blood carries an expiration date of seven days.

To augment the supply of blood forwarded from the base, evacuation hospitals maintain their own unit blood banks. Responsibility for the supply of type specific blood other than "O" rests upon the individual hospital.

The initial wound operation is directed toward the prevention of infection by a complete excision of tissue devitalized by the missile. Procedures such as closure of a sucking wound of the chest or suture of a perforation of a hollow viscus restore physiologic equilibrium as well as arrest the dangers of infection. Recognition of all devitalized tissue is often times impossible, particularly in a massive wound or one complicated by skeletal injury. Disturbances of blood supply and subtle changes that indicate impending death of tissues may not be detectable. In a certain number of these cases mixed anaerobic infection of residual dead tissues is the inevitable sequela. Others will develop invasive infection spreading from the wound to involve normal tissues. To minimize the incidence and hazards of infection, primary closure by suture is strictly avoided. Exact maintenance of the reduction of fractures by precise methods is precluded by the necessity for evacuation to the rear, so temporary or transportation splinting, usually with plaster of paris, is employed.

Chemotherapy is initiated in the field by local and oral administration of sulfonamides. The value of this procedure is questioned by many surgeons of experience. Preoperative penicillin therapy is started on all but the lightly wounded casualties on admission to hospital in the forward area. At operation, topical application of penicillin is carried out only in wounds penetrating the meninges, serous cavities and joints. Parenteral administration is continued beyond the period of the likelihood of infection or until established infection has been controlled. No patient is held in the forward area solely for the purpose of continuing penicillin therapy.

Just as plasma is not a substitute for whole blood in resuscitation, neither are sulfonamides and penicillin substitutes for the surgical excision of devitalized tissue. Chemotherapeutic agents cannot sterilize dead, devitalized or avascular tissues nor do they prevent the septic decomposition of contaminated blood clot.

In this war there have been two quite different approaches to the application of chemotherapeutic agents to military surgery. The first would utilize these agents to permit delay in wound surgery, and minimize the completeness of the excision of dead tissue. The second employs chemotherapy to extend the scope of surgery and achieve a perfection in results previously considered impossible. The latter policy has guided the surgery of the Mediterranean Theater. To reiterate the axiom that penicillin is not a substitute for surgery is not enough. Every surgeon must learn that chemotherapy opens new and startling possibilities in wound management.

The magnitude of the surgical problems that confront the forward surgeons when supported by adequate resuscitation therapy is difficult to visualize by one not having a first-hand acquaintance with their work. Highest standards of precision must be maintained if the potentialities of surgery

are to be realized to full advantage. This precision must be attained in the use of the adjuncts to surgery as well as in operative technics. Initial surgery cannot be carried on as a hasty, slap-dash and bloody spectacle, with rapid evacuation of the patient to the rear if satisfactory results are to be achieved. The average operating times for certain types of cases recorded at an evacuation hospital were: one hour 49 minutes for penetrating wounds of the head; two hours for wounds of the abdomen; two hours and a half for wounds of the thorax. Many casualties have multiple wounds that require several major procedures in sequence or simultaneously. Postoperative care is as important as the operation and may demand holding the patient for ten days or longer.

Triage at the divisional clearing station based on the urgency of the wound and the condition of the casualty establishes a "three-point forward system," as described by Jolly in the Spanish Civil War. This provides a small surgical hospital for first priority casualties—in this theater a single platoon of a field hospital reorganized and equipped for this specific mission. Other casualties of less urgent types are transferred back to the chain of Evacuation Hospitals. An important modification of the system has placed the Field Hospital Platoon in physical conjunction with the clearing station triage point. This provides for the immediate transfer of wounded from the clearing station to the first priority surgical hospital by hand litter. No pause is required for resuscitation or interference with splinting or dressings. Expert surgical management that embraces resuscitation, operation and prolonged postoperative care, becomes immediately available. Cases with a continuing source of shock that cannot be made transportable without an operation are thus salvaged and the desperately wounded receive expert care as far forward as it can be provided.

Surgeons assigned the responsibility of caring for the wounded in a first priority surgical hospital must be highly trained and experienced, as their tasks are the most exacting of military surgery. The Auxiliary Surgical Group has been found ideal as a source for this personnel. The experience of the individual surgeon is augmented in the base during periods of an inactive front. Unity and uniformity in the control of this portion of forward surgical personnel has produced a high level of competence as well as economy in the deployment of specialized surgical skill and talent. If the achievements of surgery in this theater are ever judged noteworthy, they are attributable to the fact that expert rather than inexperienced surgeons are doing the work. All other measures are ancillary items.

A well-run first priority surgical hospital exerts a remarkably favorable effect on the morale of combat troops and their officers. The divisional medical service receives a stimulus to maintain its arduous task by first hand evidence that the lives of the most desperately wounded may be saved by skillful first-aid measures and rapid evacuation. Splinting is improved, the use of plasma in Aid Stations is increased and the temptation for clearing

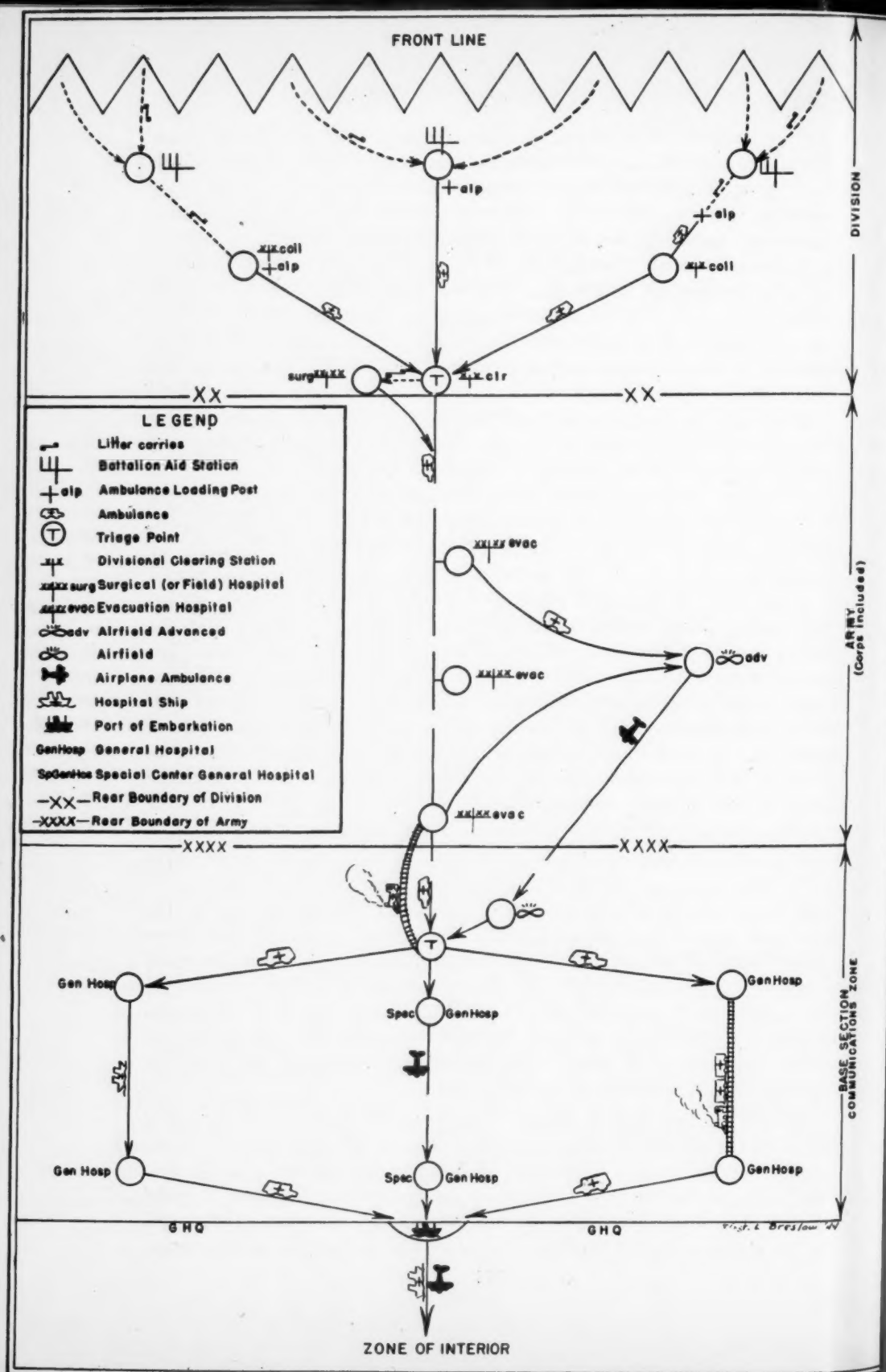

FIG. 1.—Diagrammatic representation of an Overseas Theater.

or collecting companies to indulge in heroic surgical procedures for which they were never designed or equipped is removed.

Evacuation hospitals handle the great bulk of the wounded in the forward area, as the small group of first priority cases diverted to the Field Hospital Platoon constitutes approximately one-thirteenth of the total number. These institutions, with trained and experienced professional staffs, have attained a high degree of proficiency in the procedures of initial wound management and remain the backbone of the Army medical service.

REPARATIVE SURGERY

A highly significant and far-reaching advance in military surgery has taken place in the base hospitals with the development of what may be called *reparative surgery*. Wounds left unsutured at the initial operation are routinely closed by suture, usually at the time of the first dressing. With the use of penicillin as a safeguard against infection, the management of wounds complicated by fracture or joint involvement has been revolutionized. Surgical procedures in special fields of surgery—thoracic, craniocerebral, abdominal—have also been radically altered by the application of similar principles. The significance of this development and its effect on returning an increased number of wounded soldiers to duty and in preventing deformity, disability and death in the seriously wounded can hardly be overestimated.

Reparative surgery is not to be confused with the reconstructive surgery of the Zone of the Interior. Reparative surgery is designed to prevent or cut short wound infection either before it is established or at the period of its inception. Once established, wound infection is destructive of tissue and at times of life. In many instances it permanently precludes the restoration of function by the most skillful reconstructive efforts.

If the initial wound operation has been a complete one, wounds of the soft parts may be closed by suture on or after the fourth day. The dressing applied in the evacuation hospital is removed under aseptic precautions in an operating room of a general hospital at the base. Following closure, the part is immobilized preferably by a light plaster encasement, or if this is impractical, by bed rest.

Decision to close a wound by suture is based solely on an appraisal of the gross appearance at the time of removal of the dressing. Preliminary qualitative or quantitative bacteriologic analysis of the flora of the wound by smear or culture does not provide information pertinent to this decision or allow the prediction of the result. "Clean" wounds that heal by first intention after delayed closure may show a profuse and varied flora, both anaerobic and aerobic. Identification of species and tests for pathogenicity would require weeks of arduous laboratory procedure.

It is estimated that during the Italian Campaign alone, at least 25,000 soft-part wounds have been closed on the basis of gross appearance only. Healing has resulted in approximately 95 per cent, and no loss of life or limb or serious complications have been reported. Residual dead tissue in a

deep recess of the wound is the most common cause of the failure in the 5 per cent that may be classed as unsuccessful closures. If the suture is not successful because of infection, appropriate studies and corrective therapy is instituted before resuture is attempted.

The presence of residual dead tissue or established invasive infection at the time of the first dressing is evidenced by discharge of pus and redness

FIG. 2.—Platoon of a Field Hospital acting as a forward surgical hospital with Fifth Army in Italy.

and edema of the wound margins. When these are present but minimal, the wound is allowed to "clean up" with moist dressings. Surgical excision of devitalized fragments or removal of retained foreign bodies may speed this process. Secondary closure may then be performed after a few days. If established infection is severe, or if the patient is toxic or anemic, a course of

FIG. 3.—Initial wound surgery for first priority cases at the rear boundary of the divisional area. Surgical team operating in a Field Hospital Platoon.

FIG. 5.—Evacuation Hospital with Fifth Army in Italy—December, 1943.

FIG. 6A

FIG. 6B

FIG. 6C

FIG. 6.—Reparative surgery of soft-part wound of axilla:

(A) First dressing at base hospital four days following initial débridement in forward evacuation hospital.

(B) Closure of wound by secondary suture with advancement of skin flap into axilla.

(C) First-intention healing 12 days after suture; 16 days after wounding.

FIG. 7A

FIG. 7.—Reparative surgery of wounds compounding fractures of both bones of the forearm and fracture-dislocation of the humerus.

(A) First dressing at base hospital on fifth day. Secondary anemia corrected by 1600 cc. of whole blood. Penicillin therapy.

(B) Screw fixation of comminuted head of the humerus following open reduction of dislocation.

(C) Reduction of fracture of both bones of the forearm with wiring at fracture site of the radius. Application of skeletal traction.

(D) Wound closure.

(E) Postoperative skeletal traction.

FIG. 7B

FIG. 7C

FIG. 7D

penicillin therapy and blood transfusions is instituted and followed by radical wound revision with staged closure.

The topical use of sulfonamides appears to contribute nothing to the favorable results of reparative wound surgery. Parallel series of closures show as satisfactory or better results without the topical application of sulfonamides at the time of suture, as with it. Penicillin therapy is entirely unnecessary as an adjunct to the usual reparative surgery of soft-part wounds. It is used parentally for cases of established infection and in the reparative surgery of complicated wounds.

FIG. 7E

The reparative surgery of complicated wounds, including those with extensive muscle damage as well as those with skeletal or joint injury and penetration of the viscera, is a more major undertaking. It is in this group that both the incidence and hazards of infection may be expected to be greater. It is this group of cases that is kept on penicillin therapy during the interval between initial and reparative surgery and so maintained until the likelihood of infection is past. Immediate correction of secondary anemia on arrival at the base is an essential part of the program as the days are few during which the anemia from the initial blood loss may be projected into the anemia of chronic infection and indolent wound healing. The procedures of reparative surgery are frequently of great magnitude and the patients must be adequately supported by whole blood transfusions before, during and subsequent to operation.

Compound fractures are removed from transportation splints, the wound is revisioned for further removal of devitalized tissue, reduction of the fracture is secured and maintained by skeletal traction, internal fixation or other means as indicated. The original débridement incisions directly compounding the fracture site are closed by suture. Dependent stab wound drainage to the fracture site is usually established for a limited period of time.

Open arthrotomy is carried out for impending or early joint infection. Devitalized cartilage and retained foreign bodies are removed and the joint space closed. In a few cases when serious trauma or early established infection has irreparably ruined the joint architecture, resection of the joint

FIG. 8A

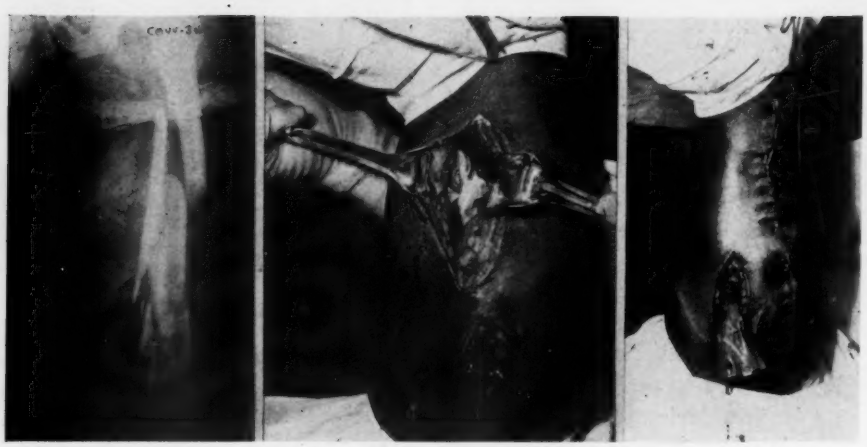

FIG. 8B FIG. 8C FIG. 8D

FIG. 8.—Reparative surgery of compound fracture of the femur.

(A) Suspension for operative access at the first dressing on the sixth day following initial débridement in a forward hospital. Anemia corrected by transfusion, penicillin therapy.

(B) Comminuted fracture as received at the base following evacuation to the rear in a hip spica encasement.

(C) Revision of the fracture site, with removal of residual devitalized bone fragments.

(D) Closure of débridement incisions; establishment of posterior dependent drainage; wire inserted for skeletal traction.

has been performed and satisfactory healing in a position of maximum usefulness achieved.

Radical management of massive organizing hemothorax by thoracotomy,

evacuation of the clot and decortication of the lung has proved its effectiveness in returning soldiers to duty and appears to have diminished the incidence of empyema. The same procedure applied to established posttraumatic empyema with penicillin therapy as an adjunct, is followed by immediate healing with a fully expanded lung. It is no longer acceptable to hold that a patient with a penetrating chest wound is making satisfactory progress as long as empyema has not made itself manifest. The focus has been changed from

FIG. 9.—Reparative surgery of thoracic wounds.

Five patients, all with severe mixed infection empyema of residual hemothorax following débridement of wounds of the chest in the forward area. Varying degrees of pulmonary collapse and fibropurulent loculation of pleural space. Without preliminary drainage, thoracotomy with decortication of the lung performed on 9th, 16th, 21st, 21st and 21st days after wounding. Penicillin therapy, parental and topical. Complete primary healing, with fully expanded lungs—ready for rehabilitation to duty status.

the management of posttraumatic pleural infection to the preservation of lung function. In the history of military surgery this will stand as one of the significant advances of World War II.

Early closure of small intestinal fistulae is a life-saving measure. Repair of exteriorized segments of large bowel returns a certain number of soldiers to limited duty and simplifies the nursing problems of the evacuation of others to the Zone of the Interior. Loop-sigmoid colostomy as an adjunct to the management of wounds of the perineum and anal regions has permitted early secondary suture followed by closure of the colostomy and return to full duty.

Skin loss in wounds comes from the missile, the over enthusiastic surgeon or infection. Skin defects attributable to tangential hits or the tearing action of the missile at the wound of exit are repaired by skin grafts as early as the

fourth day following injury. In facial injuries, splinting of the bony parts and primary suture of soft parts with provision for drainage at the time of initial surgery is followed by meticulous wound management on arrival at the base. It is believed that there is a material reduction in the incidence of disfiguring mutilations. Extensive loss of skin and soft parts attributable to the missile is not commonly observed, and it seems likely that many of the facial mutilations of warfare are attributable to loss of tissue by sepsis and contracture—both preventable.

FIG. 10.—Tangential wound of calf producing skin and soft-part defect measuring four by five inches. Secondary débridement at base hospital on twelfth day following initial débridement. Immediate split-thickness skin graft. First dressing shown five days later (17 days after wounding). No chemotherapy for reparative surgery.

Revision of craniocerebral wounds when there is evidence of residual devitalized tissue or impending infection is followed by closure when feasible even if established infection is disclosed. Observations are being made relative to the earlier repair of peripheral nerve injuries. This is a procedure that may better be considered as early reparative surgery rather than late reconstructive surgery. The projected method of management includes revision and appraisal of the nerve injury at the time of secondary wound closure and in suitable cases repair as soon as satisfactory healing is established (two and one-half to three weeks).

To realize fuily the potentialities of reparative surgery requires the introduction of a new concept in the organization of military surgery. The time-lag between wounding and initial surgery referred to as "the golden period"

has been greatly reduced by the organization of medical service in the forward area to this end. The time-lag between initial surgery and reparative surgery has now assumed an equal degree of importance. Just as every hour added to the time-lag between injury and initial surgery increases the loss of life and limb, so does every day added to the time-lag between initial and reparative surgery. Four to ten days is the "golden period" to close wounds, reduce and fix fractures, remove retained missiles and carry out other procedures to prevent or abort infection. To fail to take cognizance of the potentialities of early reparative surgery at the base in the future plans and operations will be as unthinkable as a failure to plan for the removal of the wounded from the field of battle.

Air evacuation between Army and Base, early establishment of general hospitals in close support of an advancing Army, sorting of casualties on arrival at Base so they may have the benefit of expert and specialized surgical management, are matters of administrative import. Education of surgeons to undertake new and unfamiliar procedures; the correction of anemia by whole blood transfusion so that essential surgery may be undertaken at an early date and increased attention to rehabilitation procedures are some of the major problems faced by professional personnel.

Particularly important is the concept that the surgical management of a wounded soldier from the field of battle to his ultimate hospital disposition within the theater demands continuity of policy and effort. A wounded man is not like a box of ammunition or a crate of rations that can be deposited at the boundary of an echelon and responsibility dismissed. Only by co-ordination of policy and methods between echelons can military surgery attain its full stature.

It is a satisfaction to note the contrast between the present concept of wound management and the doctrines in vogue scarcely a year ago. The closed-plaster management of wounds and fractures was designed to conserve life but exacted a high price in skeletal and soft-part deformity. Its use is now limited to certain cases with established infection of bone or with massive defects of soft parts compounding a fracture site. Recommendations that minimized the necessity for a complete initial wound operation or sought to delay it (wound trimming, "salting down with sulfa drugs," *etc.*) accepted suppuration as inevitable in a considerable proportion of cases and relied on chemotherapy to hold sepsis within bounds. Resuscitation measures that relied on plasma alone to compensate for loss of whole blood prolonged life but tied the hands of the surgeon in the performance of life-saving surgery. These and other earlier concepts were but faltering steps toward what will emerge as the ultimate scope of surgery as developed in the present war.

VASCULAR INJURIES OF WARFARE*

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ACCOUNTS OF INJURY to blood vessels in warfare have been recorded since the beginning of history, and the attention of surgeons has of necessity been primarily directed towards their treatment because of their often fatal nature. The arrest of hemorrhage and the preservation of an adequate arterial supply to the extremities have been, in fact, the main concern of military surgeons since the dawn of recorded medical history, and numerous papers concerning vascular injuries have appeared in medical literature following every war. The number of such injuries has increased steadily, probably due to the introduction of higher velocity projectiles of smaller caliber. In addition to the ordinary wounds caused by machine gun, rifle bullets and shrapnel, a great many multiple injuries are being produced by the fragmentation of land mines, grenades and aerial bombs. These latter may produce as many as one hundred small individual wounds scattered over the body without causing death, thus increasing the chance of trauma to blood vessels. It is, therefore, to be expected that the sequelae of these injuries will be encountered more numerously than ever before. Moreover, improved methods in the control of hemorrhage, shock, and infection have preserved more individuals for subsequent observation and study.

In order to bring about more highly specialized treatment of certain surgical conditions, the Surgeon-General has established centers for their treatment. In view of the fact that Ashford General Hospital is designated as one of two centers for vascular surgery, no doubt a larger proportion of this type of injury is seen at this institution.

For descriptive purposes, vascular injuries as result of war wounds may be divided as follows:

1. Those in which the blood vessel is completely severed or in which vasospasm exists to such an extent as to so impoverish the blood supply that death of the part or useless fibrosis results.

2. Activation of previously existing blood vessel disorders or tumors, such as congenital nevi and preexisting vascular injuries.

3. Partial severance of a vessel producing a false aneurysm or arteriovenous fistula.

Numerous instances of all these lesions in varying degree have been observed, and illustrative types of each are described here in detail.

I—ARTERIAL OCCLUSION

Arterial occlusion, either complete or partial, may result from several

* Read before The American Surgical Association, May 3–4, 1944, Chicago, Ill.

factors, all traumatic in nature. A vessel may be completely severed requiring ligation, and unless collateral flow is adequate, gangrene or a condition not unlike Volkmann's ischemic paralysis will result. Similarly, the vessels may be occluded by compression of a hematoma or some infringement upon its lumen by fractured bones, or by too tight splinting or prolonged and improper application of a tourniquet. While the factor of venous occlusion in producing this state cannot be overlooked, surely the clinical manifestations, generally described as Volkmann's paralysis, do occur following arterial occlusion, as will be shown in illustrative cases.

A vessel may, likewise, be completely or partially occluded by spasm. A number of factors may bring about a reflex vasospasm and produce the picture classically described by Leriche. This may occur where only the outer wall of an artery has been injured or even in cases of trauma to adjacent tissues without actual injury to the vessel itself. While vasospasm is a natural protective response to trauma, it may be so extensive in character that death of a part or its crippling may result. It may be segmental, involving only a small portion of a vessel, or it may reflexly involve other vessels of an extremity or even produce a vasomotor imbalance of more than one extremity or even the whole body. Where the whole arterial tree of an extremity undergoes such a change interference with collateral circulation is pronounced, and under such circumstances the limb is white, numb, cold, pulseless and paralyzed. If relaxation occurs within a few hours, either spontaneously or through operative measures, the limb may return to normal, but if constriction persists, thrombosis will occur and varying degrees of trophic changes will result—gangrene or fibrosis with atrophy, stiffness of the joints, and a fixation deformity. An excellent account of these matters has been published by Griffiths[1] (1940), and, more recently, by DeBakey[2] (1944).

Case 1.—*Ischemic contracture with gangrene of right hand following severance of axillary artery; median and ulnar nerves. Thrombosis of distal brachial vessels. Suture of median and ulnar nerves. No improvement in nutrition of hand following physiotherapy.*

This soldier was struck by a machine gun bullet in the upper inner aspect of the right arm May 6, 1943. The entire arm immediately felt numb, and he was unable to use it. He lost considerable blood. He was operated upon shortly afterwards, and it was found that the right brachial artery had been severed, but it was believed that the nerves were intact. Débridement of the wound was carried out. On the second day after the operation there was considerable swelling of the entire arm from the area of the wound to the finger tips. He developed blisters in the palm of his hand, and the tip of the right ring finger sloughed off. There was superficial sloughing in the palm. He entered Ashford General Hospital October 1, 1943. At that time the gangrenous areas were practically healed, but there was sensory and motor evidence of ulnar and median nerve paralysis. The arm, forearm, and hand were atrophic, and the latter was held in a fixed flexion contracture. On October 21, 1943 exploration of the lower axilla was done (Major Barnes Woodhall). It was found that the ulnar and median nerves were completely severed, and that the axillary artery had been divided and ligated. The divided nerves were sutured. The distal end of the divided

artery could not be found. Physiotherapy by means of whirlpool baths, massage and exercises has brought about no improvement, and the hand and forearm remain fixed and atrophic (Fig. 1).

FIG. 1.—Case 1: Showing atrophy, fibrosis, and fixation of the right hand following severance of the brachial artery.

Case 2.—*Ischemic contracture following dislocation of left elbow. Probable spasm followed by thrombosis of left upper extremity vessels. Little improvement following physiotherapy.*

This soldier was injured in an airplane accident February 9, 1943, at which time he sustained a dislocation of the left elbow. Upon admission to a Station Hospital at that time no pulse could be felt in the left radial artery, but the hand was warm and slightly cyanotic. There was some anesthesia in the distribution of the ulnar nerve and no voluntary motion of the fingers was possible. The dislocation was reduced and an encasement applied which remained in place for six weeks. Two weeks later there was

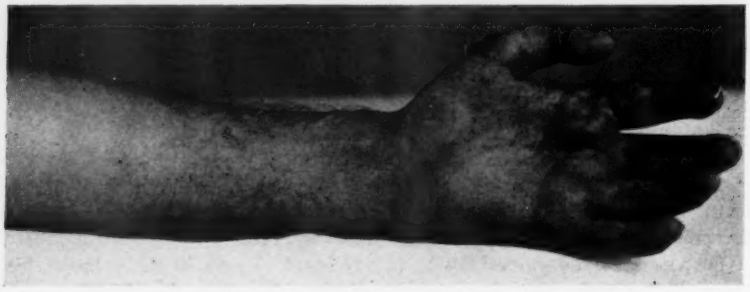


FIG. 2.—Case 2: Showing the "frozen-hand" characteristic of thrombosis of the brachial vessels.

return of normal sensation to the hand, but the patient was unable to use it. Examination at this hospital, September 9, 1943, showed an atrophy of all the muscles of the left arm, forearm, and hand. Motion of the shoulder girdle and elbow joint could be carried out but was weak. Flexion and extension of the wrist were limited to 30

degrees. The fingers were held in a slight flexion curvature and only a few degrees of motion could be carried out in them. The skin was red, slick, and atrophic (Fig. 2). No arterial pulsation could be felt in any of the vessels of the left upper extremity. Sensation was normal. Oscillometric determinations showed a "flicker" of pulsation in the midarm but none at the wrist. Physiotherapy in the form of heat, massage, and whirlpool baths has brought about little improvement.

Case 3.—*Multiple wounds of the right arm, chest, and left thigh on July 11, 1943. A-V aneurysms of left femoral and right brachial vessels. Compound fracture right elbow with ulnar, median, and radial nerve paralyses. Excision A-V fistula left femoral September 7, 1943. Rapid healing of elbow fracture under penicillin therapy. Necrosis of right forearm necessitating amputation. Excision of brachial A-V fistula.*

This 21-year-old officer sustained mortar, shrapnel and machine gun wounds of chest, extremities and back July 11, 1943. The first injury received was that of his right arm, and he immediately noticed that he was unable to move this extremity.

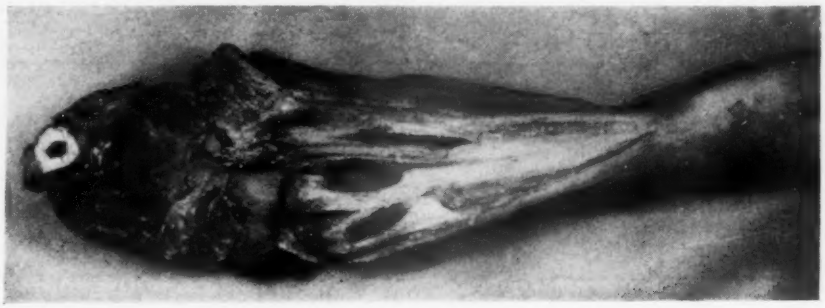


FIG. 3.—Case 3: Amputated arm showing necrosis of tendons and muscles.

Bleeding from a wound in the upper brachial region was profuse. About the same time he received a wound in the left thigh and shortly thereafter he was wounded in the right chest. Five minutes later he lost consciousness. He was immediately evacuated from the line of fire and his wounds were dressed, and he was given plasma. He regained consciousness 24 hours later. He was evacuated through hospitals to the Ashford General Hospital which he reached on September 26, 1943. The compound fracture of the right elbow was badly infected but cleared up rapidly under penicillin therapy. The arteriovenous fistula of the left thigh was successfully treated by excision on October 7, 1943. By October 19, 1943, the wounds of the elbow region were red and granulating, and a Thiersch graft was placed upon the two largest of them. Six days later the wound was dressed, and the grafts appeared to be viable. Penicillin was discontinued at this time. Three days later the temperature became elevated to 103° F. Examination at this time revealed that the entire musculature of the right forearm was necrotic, although the skin remained healthy in appearance with good arterial pulsations. Since the necrotic process appeared irrevocable, guillotine amputation was performed just above the elbow. Examination of the specimen showed that the muscles and tendons were necrotic throughout (Fig. 3). The arteriovenous fistula of the brachial vessels was excised on November 16, 1943. The stump of the amputated arm was later closed, and the patient recovered without further difficulty.

Case 4.—*Multiple wounds of back, left forearm and flank July 14, 1943. Excision of arterial aneurysms of left brachial and ulnar arteries September 6, 1943. Arterial spasm in left hand followed by vasomotor disequilibrium of all extremities, face, and trunk.*

This soldier was wounded July 14, 1943, at which time he received multiple small wounds of the left arm, left flank, and back. The larger of the wounds was débrided.

On September 6, 1943, two aneurysms, one of the lower brachial and the other of the ulnar artery, were excised on the left side. (Captain Kremer, 26th General Hospital.) One week later he began having intermittent attacks of arterial spasm in the left hand characterized by pain, cyanosis, and occasional blanching, particularly if he was exposed to cold. A week after this he noticed that the right hand became cyanotic, and this was soon followed by cyanosis of both feet, the color changes in all four extremities

'Y'

TEST SPINAL ANAESTHESIA DATE 24 February 1944

OSCILLOMETRY

CONTROL

	RIGHT	LEFT
Popliteal	7.5 at 100 mm	8.0 at 100 mm
Tibials	4.0 " 100 "	3.75 " 100 "
Foot	0.5 " 90 "	0.5 " 90 "

20 Minutes after Spinal

	RIGHT	LEFT
Popliteal	7.0 at 110 mm	6.75 at 100 mm
Tibials	6.0 " 80 "	6.0 " 80 "
Foot	2.5 " 60 "	2.5 " 60 "

SKIN TEMPERATURES

IN DEGREES FAHRENHEIT

ROOM TEMP. 76 °F.

CONTROL

	R	L
1st Toe	87.5	64.5
2d "	87.0	84.0
3d "	88.5	87.0
4th "	86.0	82.0
5th "	84.0	81.0
Plantar	84.5	83.0
Dorsum	90.0	88.0
Ankle	86.5	88.0
Midleg	91.0	91.0
Knee	87.0	88.0
Thigh	90.5	90.5

20 Minutes after Spinal

	R	L
1st Toe	92.5	94.0
2d "	93.0	93.0
3d "	93.0	93.0
4th "	92.0	93.5
5th "	92.0	94.0
Plantar	93.0	93.5
Dorsum	94.0	94.0
Ankle	93.5	94.0
Midleg	93.0	93.5
Knee	93.5	95.0
Thigh	92.5	92.5

FIG. 4.—Case 4: Showing increase in oscillations and temperature of the feet following spinal anesthesia.

increasing but at times returning to normal. On September 27, 1943, a novocaine cervical sympathetic block was performed. This produced a warm dry hand lasting for three hours. A second block on October 13, 1943, produced a Horner's syndrome, with little change in his hand or arm. He was admitted to Ashford General Hospital December 3, 1943. *There was nothing in his history to indicate any vasomotor disturbances prior to being wounded on July 14, 1943, in spite of active duty in a cold climate.*

On examination, both hands to the wrists were markedly ruborous and cold. Perspiration was increased. Both feet assumed an ever-changing pattern of color beginning on dependency, with mottled areas of deep cyanosis alternating with blotches of deep rubor. The cyanosis was seen at the terminal digits over the phalangeal joints on the plantar surface of the toes and on the medial plantar side of the feet. The remainder of the feet was deep red in color. On complete dependency the plantar portion of the

feet and toes became so completely cyanosed as to resemble the dusky grayness of impending gangrene. There were no trophic changes.

The brachial blood pressure was 130/100. All pulses were present but were weak in both feet. On elevation of the feet palor of the toes was marked on the medial plantar surfaces. His face was intensely red especially over the malar prominences. The nose had areas of mottled cyanosis and redness, and the ears were intensely red in spite of being cool to palpation. Upon light scratching of both the chest and the intrascapular regions, a typical dermatographia was elicited with wheals and erythema. Oscillometric determinations and temperature readings before and after spinal anesthesia are shown on Figure 4. It will be noted that after elimination of constriction impulses the oscillations in the tibial regions almost doubled, and the readings in the feet increased five times. The readings under spinal anesthesia were practically twice that found in the normal individual. The skin temperatures rose from five to ten degrees in the toes and feet; about three to five degrees in the legs. The readings were above those seen in the normal individual.

DISCUSSION.—The treatment of vascular occlusion, either from severance of a vessel or traumatic vasospasm, presents a problem of unusual difficulty. The final result and the ultimate prognosis will depend in the main upon the original treatment received shortly after the injury. In the first place, a tourniquet should never be applied if bleeding can be controlled otherwise, and if applied it should be as near the wound as possible. An Esmarch bandage is preferable to a rubber tube.

Every effort should be made to preserve the continuity of an artery, and in lateral lacerations repair may be possible. If ligation should be necessary, it should *not* be done in continuity but should be sectioned completely, since the division prevents peripheral arteriospasm and secures the best collateral circulation. Section and ligation of companion veins should likewise be carried out. Repair should be attempted only when it appears to be the sole means of saving a limb. Vasodilatation by means of sympathetic procaine block frequently repeated, or by sympathectomy, should be performed if the integrity of the circulation appears in doubt.

Other procedures, such as the use of plasma or blood to obtain an adequate blood pressure, the use of heparin to prevent thrombosis, and the position of the limb for maximum circulatory balance, should be employed if conditions do not otherwise contraindicate their use. In large lacerated wounds and in those accompanied by damage to other tissues such as bones and nerves, splinting is essential, but immobilization should be discontinued at the earliest possible moment and early motion instituted in order to prevent joint fixation.

In cases of traumatic vasospasm, therapy is directed to the removal of reflex vasoconstrictor impulses. This may be brought about by removal of traumatized tissue, periarterial sympathectomy or better still by procaine sympathetic block or sympathectomy.

In the late stages where contracture deformity has taken place, as illustrated by Cases 1 and 2, any progress toward recovery will be slow and the eventual outlook poor. Physiotherapy in the form of heat, massage, and whirlpool baths is indicated as are splinting and occasional plastic procedure to correct deformity.

Where vasomotor imbalance follows arterial injury, as in Case 4, the interruption of vasoconstrictor fibers by sympathectomy to one or more extremities may restore a proper balance and in any event should be tried provided there is temporary improvement following procaine block.

II—PREEXISTING VASCULAR LESIONS

It is the belief of many who have studied the subject that cirsoid aneurysms, pulsating angiomas, and arteriovenous aneurysms are essentially the same condition, all being a form of abnormal communication between arteries and veins in varying degree. It is well known that vascular nevi, congenital telangiectases, or angiomas, in which the intermediary incidence of trauma has occurred, may be the starting point of disfiguring and disabling vascular tumors. Moreover, vascular injuries, apparently dormant or inactive, may, likewise, become activated by further trauma. It is to be expected, therefore, that war injuries, either as result of direct trauma or following long continued irritation, will give rise to such conditions in increasing numbers. That twelve instances of this nature have been seen at Ashford General Hospital in the past year bear out this assumption. Four of them are cited below in detail as examples. The seriousness of this lesion as a potential hazard must not be overlooked, for an apparently innocent lesion may be the source of a disabling defect requiring major surgical procedures, including amputation. Although trauma plays the major rôle in their inception, there are probably other factors as yet unexplained which have a part in their development. When contributing arteries and outgoing veins succeed in forming diffuse anastomosis through a cavernous bed, the lesion becomes nothing more than a diffuse arteriovenous fistula. While the existence of a congenital lesion can usually be elicited from the history, this abnormality need not always be present. A wound, particularly if inflicted upon superficial vessels, such as those of the scalp, face, fingers or toes, will often give rise to these diffuse tumors, and additional trauma such as bruising or prolonged irritation may contribute further to their development. In any outspoken example of this condition the clinical picture is such a striking one that the case is likely to be reported, and there is an extensive literature on the subject. (Elkin,[3] Reid,[4] and Pemberton[5].)

Case 5.—*A small, bluish, pigmented mass in right axilla, present since childhood. Ten months trauma from rifle recoil, with marked increase in size. Complete excision and skin graft.*

This soldier is known to have a small bluish discoloration in his right axilla since childhood which had given him no trouble and which had increased only slightly in size. During ten months Army service the mass was subjected to the trauma caused by recoil of a rifle, and during that time the mass had markedly increased in size until it extended throughout the whole right axilla. Large dilated veins, easily compressible, covered an area about six inches in diameter (Fig. 5). There was no bruit and no thrill. Numerous small venules were present in the skin of this region. On December 17, 1943 skin incisions were outlined which extended beyond the dilated blood vessels. The skin of this area was completely excised as were the subcutaneous tissues, down to and including the pectoral and axillary fascia. Numerous dilated veins communicated

FIG. 5.—Case 5: Appearance of hemangioma of axilla.

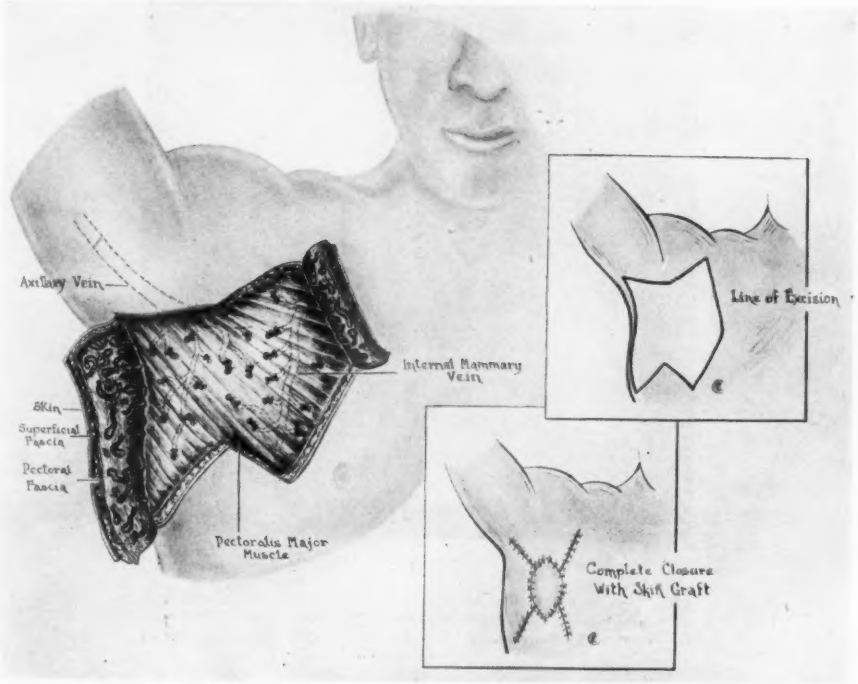


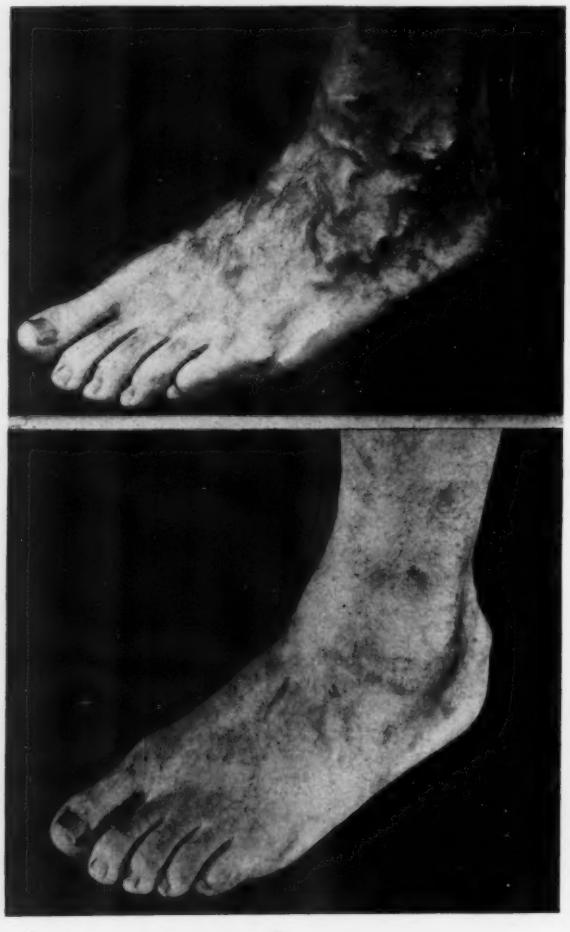
FIG. 6.—Case 5: Hemangioma of axilla showing line of excision and method of closure.

with this area and entered, for the most part, the cephalic and axillary veins. After excision the skin could be partially closed and the remainder was covered with a skin graft (Fig. 6). There has been complete recovery with no evidence of recurrence.

Case 6.—*Childhood injury, sole of left foot, by glass. Diffuse arteriovenous fistula, sole of left foot involving plantar vessels noticed 30 years after original injury following excessive marching. Complete excision of fistula after preliminary ligation of posterior tibial and dorsalis pedis vessels.*

This 37-year-old Dental Officer stepped on a piece of glass in 1914, causing a one-inch laceration in the midplantar region of the left foot. Bleeding was profuse, but healing was uneventful. In 1938 he noticed the appearance of large blood vessels over the left foot and leg. He entered the Army in December 1943 with a "waiver for varicose veins." After three weeks of basic training, at which time he underwent

A



B

FIG. 7.—Case 6: A. Diffuse arteriovenous aneurysm, sole of foot, showing marked enlargement of veins.
B. Showing appearance of the foot, one month after excision of the aneurysm.

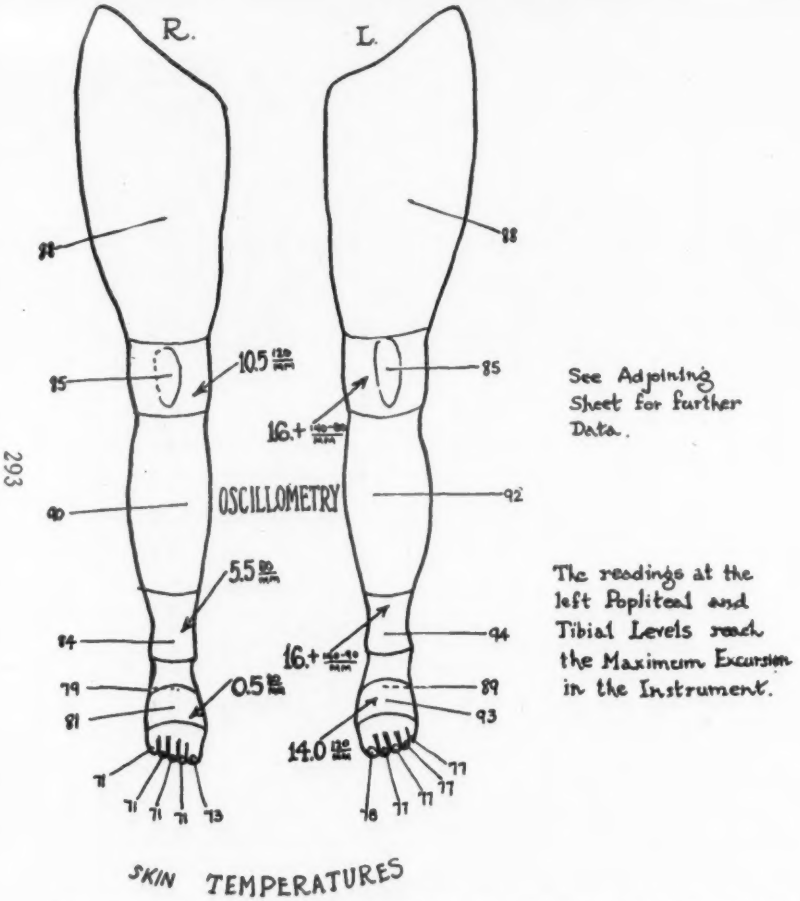


FIG. 8.—Case 6: Showing increased oscillations and temperature of left leg and foot in case of diffuse arteriovenous aneurysm of sole of foot.

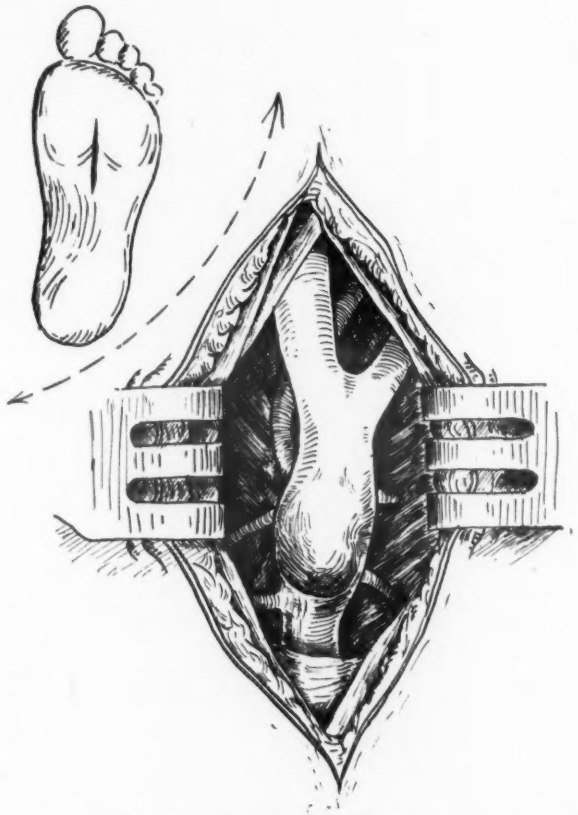


FIG. 9.—Case 6: Showing appearance of the aneurysm in the sole of the foot.

considerable marching, he noticed pain and swelling in the bottom of his foot near the toes, and on examination he was found to have a bruit and thrill in this region and was referred to this hospital. On examination there was marked engorgement of the saphenous veins over the foot and leg (Fig. 7 A). The left foot was warmer than the right. A continuous bruit, accentuated in systole, was most marked on the bottom of the foot but was transmitted to the whole leg. The posterior tibial and dorsalis pedis vessels were full and bounding. Increased temperature and oscillations of the left leg and foot are shown in the accompanying chart (Fig. 8).

It is believed that this diffuse arteriovenous fistula had its origin in the previous injury which was thought at that time to be of trivial nature. The added trauma of marching brought about a rapid increase in its development.

Operation was performed February 15, 1944. Preliminary ligation of the posterior tibial and dorsalis pedis arteries was done. The former vessel was markedly increased in size and was tortuous. A longitudinal incision was then made for three inches on the sole of the foot just medial to the old scar. Numerous small vessels were encountered. The plantar fascia was opened, and the short flexors of the foot were separated. The flexor hallucis longus was retracted medially, and the deep plantar space exposed. Several large arteries and veins, which were pulsating, together with numerous tributaries, were found in this area. Distal to this, large arteries and veins were disclosed. All of these were dissected free from surrounding tissues, ligated, and divided, and the fistula removed *in toto* (Fig. 9).

The patient's recovery from operation was uneventful. The large dilated veins previously noted disappeared in a period of about three weeks (Fig. 7 B). There has been no return of bruit and thrill, and he returned to duty May 1, 1944.

Case 7.—*Crushing injury to the left foot in 1937. No fracture. Recovery in eight months. Diffuse arteriovenous fistula, sole of left foot involving plantar vessels, noticed 1941 following marching. Complete excision of fistula after preliminary ligation of posterior tibial and three dorsal vessels.*

This 23-year-old soldier sustained a crushing injury to the left foot in civilian life in 1937. No fractures were found, and the foot was strapped. There was considerable swelling and pain for about eight months. In November, 1941, after one year in the Army, he first noticed a "humming" in his foot, with pain and swelling. He had been subjected to the strenuous activities of a soldier on Guadalcanal, and the symptoms all increased and became aggravated by marching. He entered Ashford General Hospital February 29, 1944. Examination was normal except for the left foot and leg. The left foot was slightly swollen. The superficial veins were dilated and tortuous, and a thrill could be felt over the dorsal and plantar regions, most marked on the plantar surface (Fig. 10 A). There was a loud continuous bruit with systolic accentuation over the entire foot which was transmitted up the leg to the midcalf posteriorly. The thrill and murmur could be obliterated by pressure over the posterior tibial artery. There were several pulsating vessels on the dorsum of the foot. The left foot showed increased warmth and increased oscillations (Fig. 11).

Operation was performed March 4, 1944. The posterior tibial vessels were exposed behind the medial malleolus and ligated and cut. The dorsalis pedis artery was treated in a similar manner. A longitudinal incision was made in the sole of the foot about four inches long over the region of the fourth metatarsal bone. The plantar fascia was divided longitudinally, and the small muscles of the foot were separated until the plantar vessels were reached. Large posterior tibial arteries were found entering this region and communicated with a dilated venous sac. Distal vessels, both arteries and veins, as well as lateral communications were also encountered. All of these were pulsating in spite of the previous ligations. Since they appeared to communicate with abnormal dorsal vessels, two additional incisions were made on the dorsum of the foot, and vessels in this region were ligated there. The sac, with its communicating arteries and veins, was then excised and removed after ligating and cutting all communicating branches (Fig. 12).

FIG. 10.—Case 7: A. Showing engorgement of veins of foot. B. Showing appearance of foot after excision of the aneurysm.

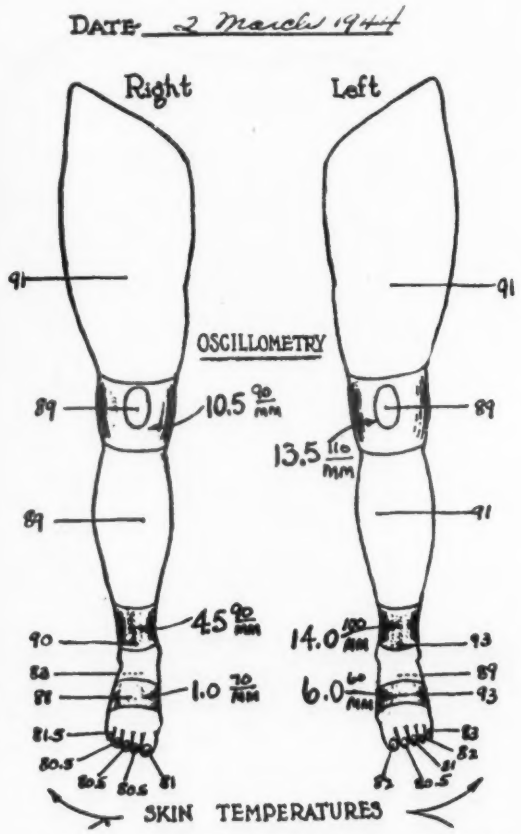


FIG. 11.—Case 7: Showing increased oscillations and temperature on the left.

All wounds were closed with silk. At the end of operation there was no evidence of a bruit or thrill, and the toes were warm and pink. There has been no return of the bruit and thrill, and the dilated veins about the foot have disappeared (Fig. 10 B).

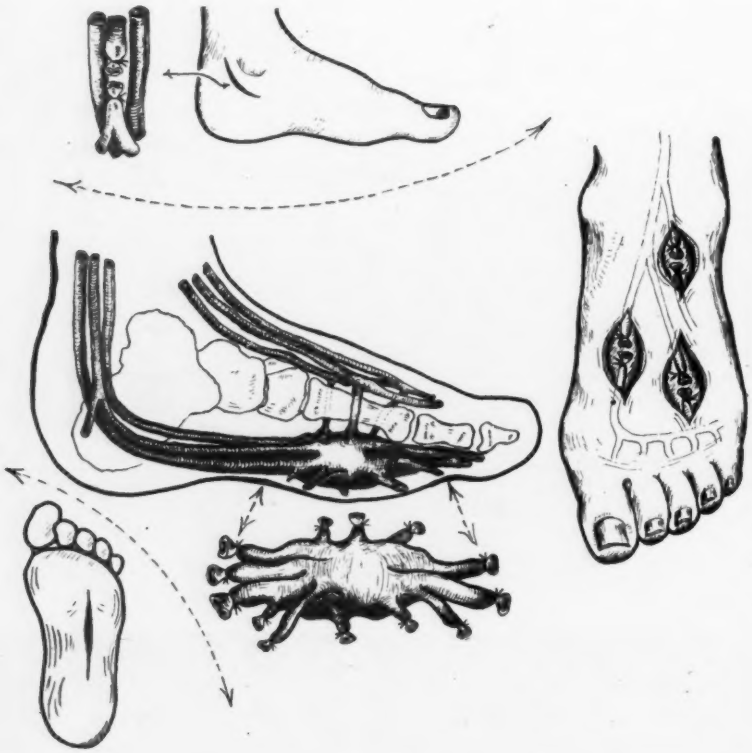


FIG. 12.—Case 7: Showing, schematically, the preliminary ligation of vessels and complete excision of the lesion.

Case 8.—*Small hemangioma, sole of right foot since childhood. In July, 1943, the foot injured by jumping into a fox hole, followed by gradual increase in size of tumor. Unsuccessful attempt to excise tumor. Severe hemorrhage necessitating amputation.*

In infancy it was noted that patient had a mass on the plantar surface of the right foot. It caused no discomfort and did not limit his activity. At age 12, it was noticed that the right leg was slightly longer than the left. Six years before entrance into this hospital he noticed prominence of the veins of the left foot and ankle. On July 25, 1943, in action in Sicily, he struck the plantar surface of his foot when he jumped into a fox hole. Following this there was pain and gradual increase of the swelling on the plantar surface of the foot. On August 10, 1943, an unsuccessful attempt was made to remove the tumor, and the posterior tibial artery was ligated.

On examination at Ashford General Hospital there was an expansile, pulsating, compressible mass involving the whole sole of the right foot, extending from the heel to the toes (Fig. 13 A). There was a continuous thrill and bruit over this area accentuated in systole. The veins of the right leg were dilated. The right foot was warmer than the left, and the right leg was 6 cm. longer than the left. There were marked increased oscillations on the right side.

On December 20, 1943, an attempt was made to excise the aneurysm after ligation of the posterior tibial and dorsalis pedis vessels. The whole plantar surface was a mass of dilated venous and arterial sinuses. Hemorrhage from them could only be controlled with a tourniquet and, after a three-hour attempt to ligate them individually and *en masse*, it was felt that any procedure other than amputation might prove fatal. Amputation was accordingly performed.

Injection of the arterial tree of the amputated foot is shown in Figure 13 B. Even after ligation of a large number of vessels, numerous dilated sinuses are still present.

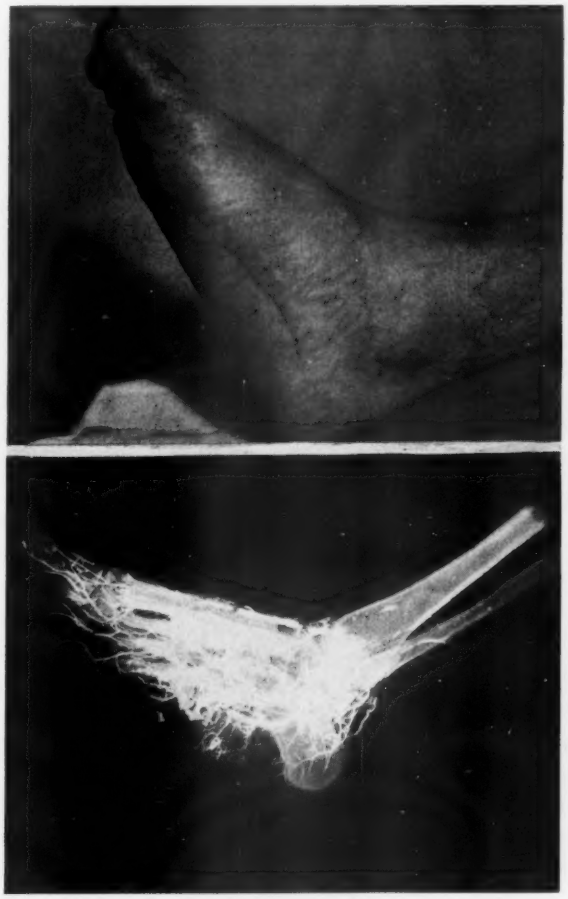


FIG. 13.—Case 8: A. Appearance of the foot before final operation. The posterior tibial artery has been ligated and unsuccessful attempt made to extirpate the lesion.
B. Arteries of the amputated limb injected with mercury. Note numerous collaterals about the points of ligation and the increased vascularity of the whole foot.

DISCUSSION.—A variety of operative procedures has been employed in the treatment of these conditions—ligation of the main blood supply; multiple circumferential sutures; obliteration of the lesion with the cautery; or injection of thrombosing or scar-forming sclerotics. The only universally suc-

cessful method is complete extirpation, since recurrence notoriously follows halfway measures. Moreover, operation should be carried out in the early stages of the development of the lesion. Otherwise the rapidity of its growth and the extent of involvement may place its removal outside the domain of surgery or else require sacrifice of a part, as illustrated in Case 8. Under any circumstances, the operator is confronted with a problem requiring not only meticulous skill and care in its performance, but one demanding the courage to attempt an ordeal which may be fatal because of hemorrhage, or which may require amputation.

III—ANEURYSMS

It is not the purpose of this paper to discuss in detail the diagnosis and treatment of aneurysms or arteriovenous fistulae. Openings in blood vessels produced by small missiles may for a time present no symptoms and no physical signs other than a bruit. For that reason these lesions are frequently overlooked, particularly if more striking or extensive injuries are present. The value of auscultation as a means of determining the presence of these lesions cannot be too strongly stressed. In the inception of any vascular injury, external or internal bleeding may be severe, and the immediate care quite correctly is directed to the control of hemorrhage. On the other hand, bleeding may be slight, even though a major vessel is involved, and in the absence of severe laceration it may be controlled by pressure of the soft tissues and thus a pulsating hematoma or false aneurysm be formed. In the presence of a large number of casualties and under battle conditions, such as front line hospitals are now working, a diagnosis, though incomplete, or even incorrect, may be carried by a wounded soldier for some time. This does not imply that proper treatment has not been given, but it does entail upon those who are working in the Zone of Interior or in general hospitals distant from the battle field the necessity of careful examination uninfluenced by any previous diagnosis. Moreover, it is a well known fact that a vascular lesion may develop slowly to the point of recognition. For example, an arteriovenous fistula present from the onset of an injury may not show characteristic signs until edema and tissue hemorrhage have been absorbed. It is well to remember that blood vessels are usually accompanied by nerves, and that nerve lesions, which are so striking in their immediate manifestations, may mask or cause to be overlooked accompanying blood vessel trauma. Inconspicuous wounds may, likewise, involve blood vessels and are frequently overlooked through failure of the examining surgeon to suspect their presence, or because his attention has been directed elsewhere to a seemingly more important lesion. Aneurysms of various types will be overlooked unless *every* wound is carefully examined, particularly by auscultation.

The differentiation of a false arterial aneurysm and an arteriovenous fistula is of extreme importance since the sequelae, the general and local effects, as well as the treatment of the two conditions, differ greatly. The differential diagnosis is not always easy but as a rule an arteriovenous com-

munication is characterized by a *continuous* thrill and a *continuous* machine-like bruit accentuated in systole, whereas, in the false aneurysm there is a slight but distinct pause between the systolic and diastolic phases, or the bruit may be heard only in systole. In the case of a fistula the swelling is usually less pronounced although some fistulae communicating through a false sac may give rise to a tumor of considerable size.

The dilatation of veins about and distal to a fistula, the slowing of the pulse following its obliteration, and the trophic changes resulting from an impoverished blood supply distal to it are further differentiating points. In large fistulae or in those close to the heart, cardiac dilatation with subsequent failure is likely to follow. While time should be allowed for the development of collateral circulation, operation should not be delayed until cardiac failure has supervened. The enlargement of the heart and its rapid return to normal size following excision of this lesion are strikingly shown in Figures 14 and 16.

Case 9.—*Femoral A-V fistula, resulting from rifle bullet on September 21, 1943. Cardiac enlargement with beginning failure. Excision of fistula. Rapid return of heart to normal size.*

This 21-year-old soldier was struck by a through-and-through rifle bullet in the right thigh September 21, 1943. There was very little bleeding. The wound was dressed shortly afterwards, and healing took place in about ten days. About one month afterwards he noticed fullness and swelling in this region, and about that time the presence of an aneurysm was noted.

He entered Ashford General Hospital February 5, 1944. There was some swelling of the right thigh, particularly on the inner medial aspect. In this region a distinct continuous thrill could be felt. He complained of fullness in the right thigh, swelling of the right lower extremity, pain in the right leg on walking, and dyspnea on exertion. The swelling of his thigh was most marked on the inner and middle aspects. The whole leg was swollen, and there was pitting edema of the right ankle. The veins of this leg were enlarged. A distinct thrill could be felt over the whole inner aspect of the thigh. A bruit, most marked in this region, was transmitted up to the groin and downward to the midleg. It was continuous but accentuated in systole. Obliteration of the femoral artery by pressure reduced the pulse rate from seventy-eight to forty-eight. Roentgenogram of the heart showed left ventricular enlargement (Fig. 14).

On February 9, 1944, quadruple ligation and excision of the fistula were done. The proximal artery was greatly dilated as were all the veins in the region of the fistula. The distal artery was small. Numerous collateral vessels were found in the region of the fistula. All vessels in this region were tied and cut, and the fistula was completely excised (Fig. 15). Postoperative course was uneventful. Roentgenogram of the heart made one week after the operation showed that the heart had returned to normal size (Fig. 14).

Case 10.—*A-V aneurysm, right posterior tibial vessels with communication through interosseous membrane. Ligation of all communicating vessels. Obliteration of fistula by multiple mattress sutures. Recovery.*

This soldier sustained a bullet wound of the right leg on March 31, 1943. The missile entered the posterolateral aspect of the leg five inches below the knee and made its exit on the inner lateral aspect. Bleeding was profuse but was controlled by a pressure bandage. On April 2, 1943, an incision was made on the anterior surface of the leg, and he was told that an artery was ligated. There was a partial paralysis of the peroneal nerve which had largely disappeared by October, 1943. In November, 1943,

the presence of an arteriovenous fistula was noted, presumably of the posterior tibial vessels, and he entered Ashford General Hospital December 1, 1943. Examination on admission was negative except for the right leg. The leg was swollen from the knee downward, and there was pitting edema of the ankle. An expansile pulsation was present in the area just below the popliteal space and in the line of an old incision on the anterior surface between the tibia and fibula six inches below the knee. In both areas there was a continuous thrill and a loud continuous bruit accentuated in systole. The bruit was transmitted over the whole leg, foot, and thigh. Obliteration of the

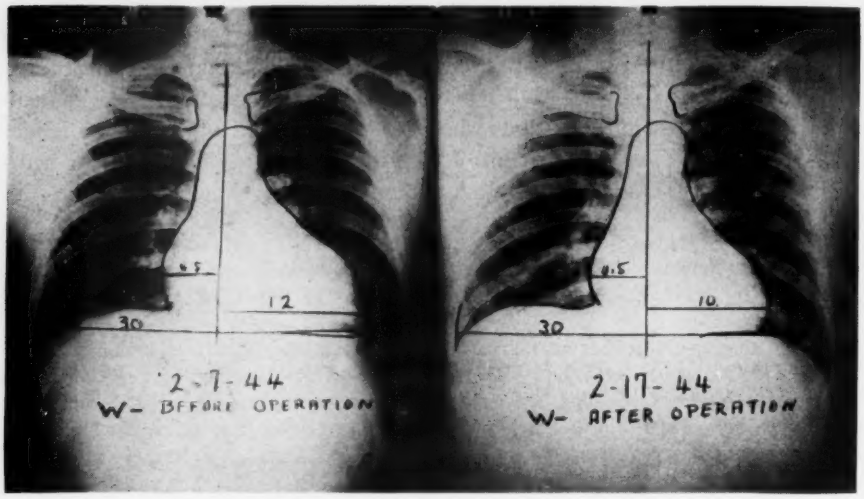


FIG. 14.—Case 9: Showing enlargement of the heart and rapid return to normal following excision of arteriovenous fistula.

popliteal artery by pressure reduced the pulse from 94 to 80. Neurologic examination was negative except for slight weakness of the extensor hallucis longus, the tibialis anticus, and hypesthesia over the lateral aspect of the foot. Oscillations were markedly increased in the whole right lower extremity. Examination of the heart showed moderate left ventricular enlargement (Fig. 16). Operation was performed December 15, 1943. Incision was made in the popliteal space and continued downward to the midcalf. The popliteal artery and vein were identified and temporarily occluded with a ligature. Both vessels were markedly enlarged. Another incision was made over the course of the anterior tibial vessels overlying the interosseous membrane at its upper end, and a large pulsating sac was uncovered in this region which apparently communicated through the membrane with the main sac on the posterior surface of the leg. The posterior incision was then dissected further, and a large sac into which numerous communicating arteries and veins entered was found. All of these vessels were separately ligated and cut, as were the proximal vessels previously identified. In an attempt to remove the sac in its entirety severe bleeding was encountered, evidently arising from other communications. This bleeding could not be controlled by individual ligation of vessels, and the whole sac was, therefore, obliterated and infolded by a number of heavy mattress sutures. This controlled the bleeding and obliterated the bruit and thrill. The wound was closed with silk. The patient's recovery was uneventful, and he returned to duty April 1, 1944. Enlargement of the heart previously noted returned to normal (Fig. 16).

Case 11.—*Left brachial aneurysm following gunshot wound. Paralysis of median, radial, and median cutaneous nerves from pressure. Complete division of ulnar nerve. Excision of aneurysm. Suture of ulnar nerve.*

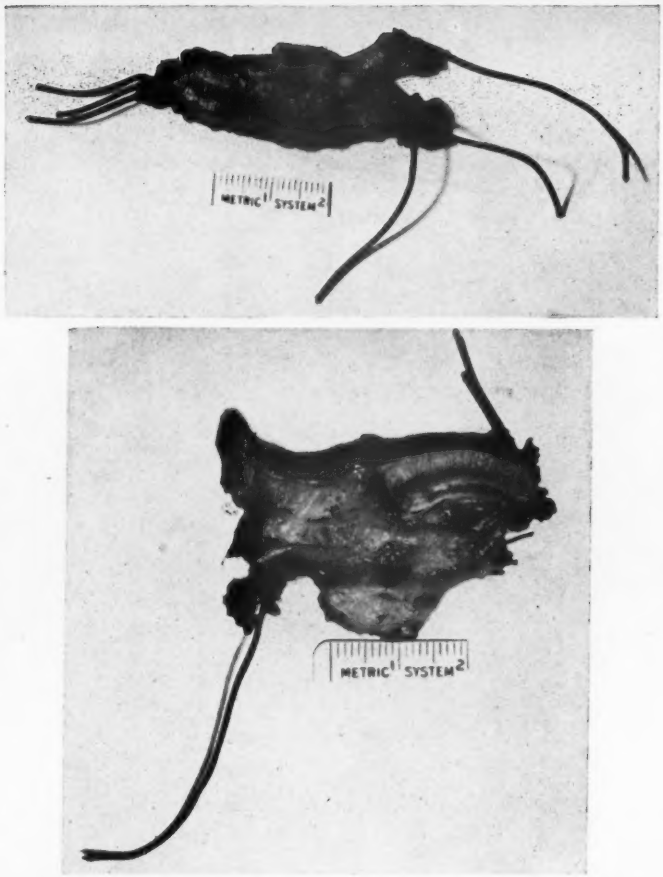


FIG. 15.—Case 9: A. Arteriovenous fistula excised.
B. The fistula opened showing the artery (above) communicating with the vein through a common sac.

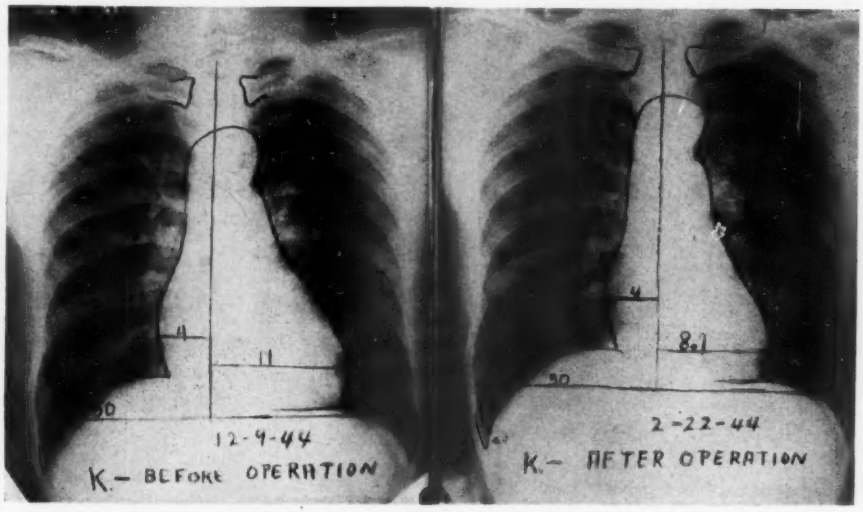


FIG. 16.—Case 10: Showing enlargement of the heart and return to normal size following excision of an arteriovenous aneurysm.

This patient was wounded, November 19, 1943, by fragments of artillery shell. He received wounds in the left shoulder, left arm, and left hand and face. There was considerable bleeding from the wound in the left arm which was situated just below the axilla. He immediately noticed numbness of the hand and inability to use it. He was evacuated from the line of fire, and his wound were débrided and an encasement applied. He was eventually evacuated through hospitals to Ashford General Hospital where he arrived March 9, 1944.

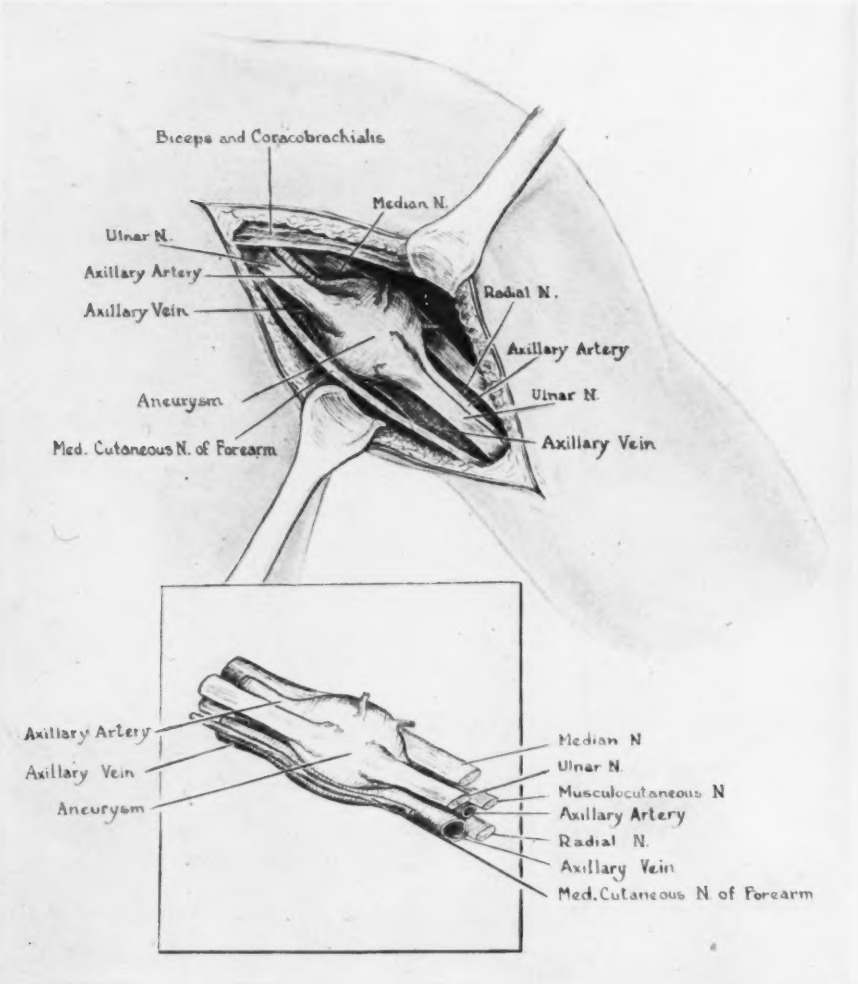


FIG. 17.—Case 11: Showing aneurysm of brachial artery with severance of the ulnar nerve and pressure paralysis of other nerves in this region.

At the time of admission all the wounds were healed. Aside from the left upper extremity, examination was unimportant. In brief, examination showed complete paralysis of the median and ulnar nerves and a partial paralysis of the musculocutaneous and radial nerves. Along the medial aspect of the upper third of the left arm was a scarred wound measuring 8 cm. in length. In the left axilla near the anterior axillary

fold was a pulsating mass 3 cm. in diameter. There was no thrill, but a systolic bruit could be heard over it. The radial pulse was weak.

Operation was performed on March 17, 1944. An incision was made along the anterior border of the axilla, and the pectoralis major muscle was exposed and retracted upward. The vessels and nerves of the arm just below the axilla were exposed, and the proximal and distal brachial arteries connecting with the aneurysm were isolated and temporarily occluded with ligatures. The nerves in this region were firmly adherent to the aneurysm, stretched over it, and subjected to its pulsation. They were dissected

FIG. 18.—Case 12: Arterial aneurysm of axillary artery with paralysis of nerves from pressure.

free from it with considerable difficulty. It was discovered that the ulnar nerve was completely severed at the medial side of the aneurysm and that the hiatus between the severed ends was filled with scar tissue (Fig. 17). After isolation of the ulnar, median, radial, and median cutaneous nerves, the aneurysm was ligated proximally and distally and removed. The ends of the divided ulnar nerve were freshened and sutured with silk and tantalum. (Major George L. Maltby.)

Case 12.—*False aneurysm, axillary artery, following shrapnel wound. Pressure paralysis of medial, radial and ulnar nerves. Excision of aneurysm. Neurolysis. Sensory and motor improvement.*

On September 23, 1943, this officer was struck with multiple shrapnel fragments on the anterior chest wall, left elbow and left axilla. There was immediate loss of motor power of the hand and loss of sensation proximal to the elbow. There was very little bleeding, but there was considerable swelling in the axilla. There was some return of sensation in the hand and arm shortly after the injury. His wounds healed without difficulty.

He entered Ashford General Hospital December 1, 1943. Examination was essentially negative except for the left upper extremity. In the left axilla there was an oval

FIG. 19.—Case 12: Appearance of the axillary aneurysm after excision. Note groove made by median nerve.

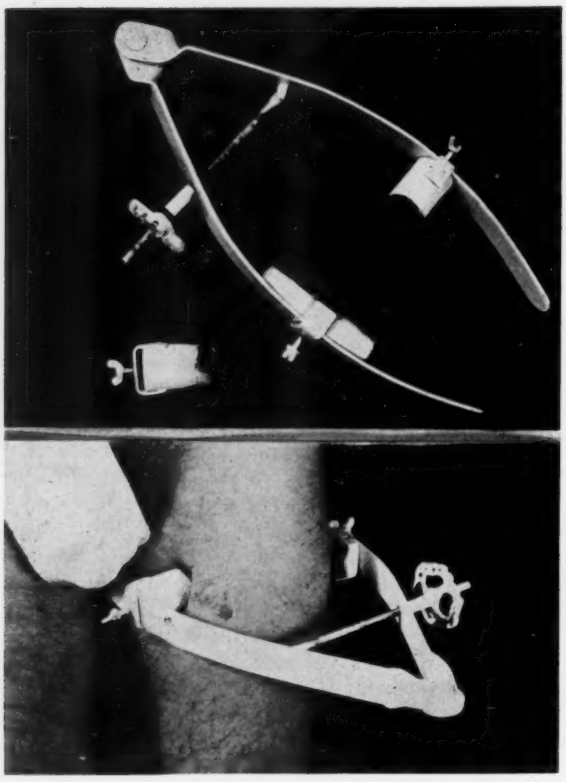


FIG. 20.—A. The Matas compressor. This is an inexpensive and easily constructed instrument.
B. The compressor in place on the femoral artery.

mass, 5 x 3 cm., which pulsated with systole (Fig. 18). There was no thrill, but a harsh systolic bruit could be heard over it. With pressure on the axillary artery above the mass the pulsation and bruit could be partially diminished. Upon tapping the mass paresthesia developed over the entire hand. The radial pulse was weak. There was hypalgesia and scattered areas of anesthesia over the peripheral distribution of the ulnar, median, radial, and medial cutaneous nerves of the forearm. Motor power of the muscles of the hand and arm was weak, and there was considerable stiffness of the joints. It was apparent that the axillary artery had been injured and was the seat of aneurysm. Neurologic examination indicated multiple nerve injuries, but of a type suggesting pressure rather than actual severance.

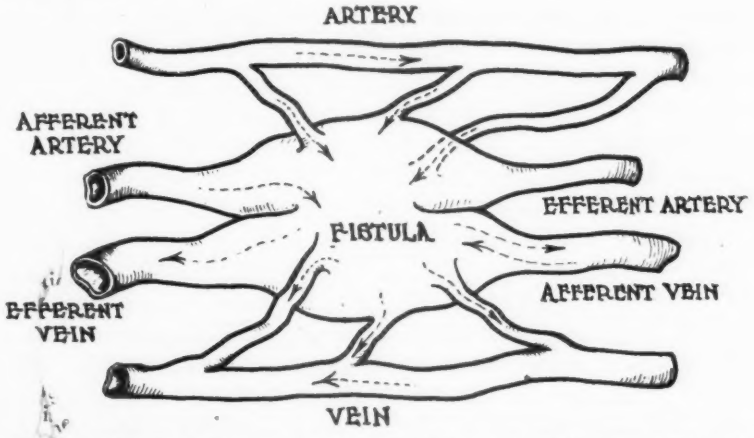


FIG. 21.—Schematic drawing to show communications of arteriovenous fistula and necessity of not only quadruple ligation but complete excision with all branches.

Operation was performed December 14, 1943. An incision was made along the anterior border of the axilla and extended down the arm about three inches. The axillary fascia was opened, and the axillary artery exposed above and below the aneurysm, and temporary ligatures were placed about the vessel. The median nerve ran directly over the aneurysm and grooved it (Fig. 19). Except for flattening and some fibrosis the nerve was normal. The ulnar nerve was adherent to the aneurysm on its medial surface and the radial nerve posteriorly. These nerves were freed from the aneurysm which was then ligated both proximally and distally and removed. Patient returned to duty as a staff officer six weeks later, and he reports that there has been a gradual improvement in the motor and sensory function of the arm and hand.

DISCUSSION.—Certain basic principles must be observed in the treatment of these conditions. Such a lesion is never a matter of emergency unless it is rapidly progressing in size, or has ruptured, or unless heart failure is impending. Time should be allowed for the development of collateral circulation about an arteriovenous fistula, usually a matter of three or four months. In an arterial aneurysm the use of artificial means to develop collaterals, usually proximal compression of vessels either manually or with the compressor devised by Matas, should be employed (Fig. 20). Where nerve lesions accompany aneurysms, complete excision of the lesion, together with neurolysis and nerve suture, should be carried out in a single operative procedure. Where *large* arterial aneurysms exist without accompanying

nerve damage the obliterative endo-aneurysmorrhaphy of Matas is the operation of choice. This type, however, is usually the result of arteriosclerosis or syphilis, and is, therefore, less often encountered in young soldiers.

The effect on the heart, the general circulation, and the part affected, demand that arteriovenous fistulae be completely eliminated. The manner of its obliteration is of importance because if the operation is incompletely performed recurrence is apt to take place. On theoretic grounds it would seem best to repair the opening in both artery and vein, but this is technically difficult and may result in secondary hemorrhage, thrombosis, or recurrence. Since collateral circulation is usually abundant, complete excision with ligation of all communicating vessels is the method of choice. Ligation without excision usually results in the recurrence since the fistula will be established rapidly through collaterals (Fig. 21). If excision is impossible because of the anatomical location as in Case 10, or because of uncontrollable hemorrhage, recourse may be made to infolding the fistula with heavy mattress sutures. The operation should be carried out with the greatest care because of the number of vessels involved and because their thinness and friability may lead to uncontrollable hemorrhage. The operation is best performed without the use of a tourniquet since individual blood vessels can be better isolated and complete excision more thoroughly accomplished. Moreover, since the operation is frequently a prolonged one a tourniquet would have to be released during the course of the procedure. Continuous spinal anesthesia has been generally employed in operations upon the lower extremity, or intravenous sodium pentothal or ether in procedures in other locations.

SUMMARY

Illustrative cases are presented showing three main types of arterial injury, namely:

1. Arterial occlusion from severance of vasospasm.
2. Blood vessel tumors and injuries activated by trauma.
3. Aneurysms and arteriovenous fistulae.

Diagnosis and treatment of these conditions are discussed.

Illustrative drawings were made by Captain J. W. Kahn, M.C., and Corporal Vincent Destro. Photography was done by Captain Floyd B. Hall, M.A.C.

REFERENCES

1 Griffiths, D.Le.: Volkmann's Ischaemic Contracture. Hunterian Lecture to the Royal College of Surgeons of England, February 2, 1940.

2 DeBakey, Michael E.: Traumatic Vasospasm. The Bulletin of the U. S. Army Med. Dept., No. 73, 1944.

3 Elkin, Daniel C.: Cirsoid Aneurism of the Scalp. Annals of Surgery, 80, 332, 1924.

4 Reid, Mont R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital. Arch. Surg., 10, 601, 1925.

5 Pemberton, John J., and Saint, James H.: Congenital Arteriovenous Communications. Surg., Gynec. & Obst., 46, 470, 1928.

DISCUSSION.—LT. COL. CLAUDE S. BECK, M.C., Cleveland, Ohio: I wish it were your privilege, as it has been mine on several occasions, to visit the Ashford General Hospital. There you would find a surgical service with surgical specialties that would compare very favorably with the surgical services of our best civilian hospitals. You would find there a group of vascular cases that, I daresay, cannot be equalled anywhere else in the world. In the operating room you would find surgical technic of the finest quality.

I might comment briefly on the incidence of arterial spasm. We are acquainted with vascular spasm developing without any history of injury, but in the military hospitals we find more cases of vascular spasm than you might appreciate.

We find cases of vascular spasm in the presence of nonpenetrating wounds. There is scarcely a small Station Hospital where I visit, where I cannot find one or more examples of mild or severe vasospasm. You will sometimes find it following a simple fracture of a long bone, and you will sometimes find very severe forms of vasospasm in the more severe wounds, the compound wounds of legs and arms accompanied by infection.

Leriche, twenty years ago, pointed out that vasospasm could be set up by a slight superficial infection, such as you might find between one's toes, and just a few weeks ago I found a patient in one of our hospitals with trichophytosis, and he had an extraordinarily severe degree of bilateral vasospasm, so severe on one foot that an ulcer of the soft tissues was present.

Colonel Elkin has referred to the importance of vasospasm in the severely wounded, and Major DeBakey recently has written a very excellent short article on vasospasm in war injuries published in "The Bulletin." Major DeBakey points out that vasospasm may be present when the penetrating wound is several centimeters away from the artery, and that a wound several centimeters from an artery may throw a major artery into complete spasm.

It is appreciated by the military personnel that vasospasm may shift the balance toward necrosis of soft tissues, that it is important to pay attention to vasospasm when it does complicate war injuries, those injuries where the major artery might be severed, or other injuries in which you have edema of tissues, or in which you have hematoma under the facial planes which may produce pressure on whatever collateral blood supply is present.

And then, of course, the surgeon must pay attention to the kind of dressing that is applied to the wound, not to put it on too tightly, to be careful in the application of plaster encasements, and also in the use of tourniquets. Vasospasm can then turn the balance towards the production of necrosis of tissues. It is also believed that vasospasm can be a factor in the development of gas bacillus infections in the soft parts.

I would like to emphasize Colonel Elkin's fourth case by referring to it briefly. This patient received a severe injury of his left arm. The wound was treated by débridement. Then, about three weeks later, two aneurysms of the left arm were excised, one of the brachial artery and one of the ulnar artery, and subsequently, after about a week or ten days, the patient showed intermittent vasospasm of the left arm. He gave no history of vasospasm preceding the injury. Then, after another interval of a week or so, intermittent vasospasm appeared in the right arm, and subsequently in his legs, and then it spread to involve the trunk, the abdomen, chest, neck, face and ears, so that starting with the left arm vasospasm spread to involve the entire vascular tree.

Sympathectomy was undertaken on the left arm and gave a good result in that arm. I am curious to find out whether it had any effect in breaking the chain of events to the other three extremities.

I saw this patient. No doubt if the chain is not broken by the sympathectomy he may need sympathectomy in the other three extremities.

Colonel Elkin, in his paper, recommends injection by novocaine or sympathectomy in those patients where the viability of the soft tissues is threatened. But as I see patients in the General Hospitals who have suffered severe war injuries, I think perhaps the

operation of sympathectomy should be extended more commonly to those patients who have severe symptoms from vasospasm without necrosis. These symptoms may be very severe.

I think perhaps in the future sympathectomy may be applied more commonly to these patients.

DR. J. D. RIVES, New Orleans, La.: I do not wish to challenge Doctor Elkin's opinion that ligation and complete excision is the most generally useful method of treatment in traumatic arteriovenous fistula, but I do wish to call attention to the fact that there are many instances in which it is either impractical or undesirable, and that in such cases the several operations of Matas are still extremely valuable. Several individuals writing upon this subject in recent years have made it apparent that the principles underlying the Matas' operations are sometimes imperfectly understood. The obliterative aneurysmorrhaphy, whether it be applied to arterial or arteriovenous aneurysm, has as its chief advantage the fact that it requires a minimum of dissection and preserves all of the collateral circulation.

I would like to show you two slides illustrating this fact. This case is one operated upon by Dr. Urban Maes, the arteriograms having been done by Dr. Ross Veal. It is a popliteal arterial aneurysm, syphilitic in origin. The first slide demonstrates the fact that the two main openings into the sac lie superficial in the popliteal space but that the sac itself is deeply placed and that the collaterals lie immediately adjacent to it. The second slide shows the conditions after a typical intrasaccular suture by the Matas method. You will see that the largest collaterals emerge from the main trunk so close to the openings into the sac that it would be quite impossible to ligate the artery without destroying them. Furthermore, dissection of the sac would have destroyed numerous other collateral channels that have, by this method, been completely preserved.

The second case illustrates the application of this method to an arteriovenous aneurysm. This patient was a young colored male who had suffered a gunshot wound of the left thigh. A huge false aneurysmal sac developed, extending from Poupart's ligament and the pubis to about the junction of the middle and lower thirds of the thigh. It contained fully two liters of blood at the time of operation. Due to the location of this sac it was impossible to secure preliminary control of the circulation. It was at first thought to be a connection between the common femoral artery and the femoral vein, but proved at operation to involve the profunda femoris. The superficial femoral artery was stretched across its wall and practically collapsed by pressure. It was ligated due to an error that resulted from an anatomic anomaly. The external iliac artery bifurcated above Poupart's ligament and the superficial femoral and profunda femoris passed separately beneath Poupart's ligament. Since obliteration of the artery by compression caused marked diminution of pulsation and thrill in the sac, the superficial femoral artery and the femoral vein were ligated before the nature of the aneurysm was recognized. The profunda femoris lay directly beneath the superficial femoral artery. If an attempt had been made to dissect out this sac and ligate its various connecting vessels I would probably have lost the patient from hemorrhage, and I would certainly have destroyed all of the most important collateral circulation to the leg. By intrasaccular suture it was possible to close the seven openings into the sac and preserve an entirely adequate collateral circulation. The technical difficulties of this procedure I shall not discuss here but I am sure that it will be apparent to you that even the intrasaccular suture was far from a simple procedure.

The third case illustrates the usefulness of the reconstructive type of operation for direct arteriovenous fistula. This patient was a middle-aged colored male who had suffered a gunshot wound of the neck which resulted in the formation of a large direct communication between the common carotid artery and the internal jugular vein immediately below the bifurcation of the common carotid. He was middle-aged

patient with damaged peripheral arteries and it seems to me apparent that under such circumstances the ideal procedure should include preservation of the common carotid artery. The transvenous suture of Matas is applicable only when it is possible to obtain complete preliminary control of circulation, which is obviously not feasible in the neck unless the artery and vein can be isolated on both sides of the communication. The proximal control in this instance was secured without great difficulty, but scarring above the fistula was so dense that every attempt to isolate the external and internal carotid arteries and the internal jugular vein resulted in active hemorrhage which could be controlled only by suture of the vein. Accordingly, the site of the arteriovenous communication was isolated and the fistula closed by means of two rows of interrupted U-sutures of silk. The vein was then obliterated by additional sutures which encircled its entire lumen. In this way, the artery was reconstructed and its function preserved. I believe that it is not only unnecessary but unwise to preserve the continuity of the involved vein because the venous collaterals are always adequate and the preservation of such a large vein after considerable trauma to its intima invites thrombosis and embolism. This operation is simply a variant of the Matas' transvenous suture, making it applicable when preliminary control of circulation cannot be accomplished. In this instance the ligation of all communications and excision of the fistula would have seriously impaired the cerebral circulation even if it could have been accomplished without undue risk. The reconstruction of the artery was not only better but easier.

I believe that these examples demonstrate the fact that the Matas operations are not obsolete. I am sure that Doctor Elkin is fully aware of these facts and probably has included them in the complete version of his paper. In the limited time it was necessary that he place his emphasis on the methods most generally useful in the type of cases seen in military hospitals. In young individuals with peripheral arteriovenous communications the collateral circulation is, I believe, always adequate, in most instances preliminary control of circulation is possible, and ligation and excision of the aneurysm is the surest and simplest method of treatment. This is unquestionably true in those aneurysms having numerous communications with a relatively small sac such as the three circoid-type aneurysms that he has described. I wish to emphasize the fact that the surgeon who attacks arteriovenous aneurysms should be familiar with all of the various methods that have been described, any one of which he may be called upon to use in an individual instance, and that it is not infrequently necessary for him to improvise modifications or combinations of these procedures after the nature of the lesions has been demonstrated by dissection.

DR. ALLEN O. WHIPPLE, New York: I had not expected to discuss this paper, but a reference to the work that Doctors Blakemore and Lord have done in this field has not been mentioned, and it seems to me that it is only fair to speak of the original work they have done.

Blakemore and Lord have devised a nonsuture method of bridging gaps in main arterial defects, which in a large series of animal experimentations has proven remarkably effective, and has been used in a sufficiently large number of clinical cases to show that it is not only feasible but readily carried out.

I regret that I have not lantern slides to show that method, but the essential parts of it are that a vein graft is threaded through a vitallium tube on two ends, and the endothelial-covered vein ends are introduced into the ends of artery that have been excised or damaged. This endothelial-to-endothelial lining permits of a reestablishment of circulation through the artery; thrombosis does not result, and the restoration of circulation to the limb is promptly reestablished.

In the animal work which they have carried out, they have excised portions of the femoral, ligated the ends, and established an infected wound; and later, between 12 and 24 hours, have reestablished circulation in that limb by means of this technic.

I have used it myself in anastomosing the splenic vein to the renal vein in the case of portal obstruction, and the patient who had been having repeated gastric or esophageal hemorrhages, and had been tapped a number of times before the operation, has had no recurrence of bleeding or of ascites for nine months.

I think Doctor Andrus, who has observed this work where it was done in the surgical laboratories of Cornell, has seen the animal work in this field, and it seems to me it is only fair to say that this is a method of reestablishing circulation in a main arterial trunk which must be considered and must be given due study and tried.

In a series of eight cases that I saw in Bizerte last summer, seven of them had come to amputation (these were injuries to the popliteal artery) and they had all been previously treated with paravertebral block.

Dr. Vilray P. Blair, St. Louis, Mo.: Did that vein that substituted for a section of a large artery dilate? If it did not, why?

Doctor Whipple: All I can say is that a vein has been used to replace segments of the abdominal aorta, and an aneurysm has not resulted. It is a very interesting example of Wolff's law, in that function apparently creates an hypertrophy and hyperplasia in the venous segment.

Lt. Col. Elkin (closing): I am very glad to have Doctor Whipple bring to the attention of this Association Doctors Blakemore and Lord's work, which of course is of extreme importance. Doctor Whipple will realize, however, that the patients which I reported here were seen anywhere from six weeks to six months after the origin of the injury, and the application of the principle at that time was hardly applicable.

In the patient which Doctor Beck discussed, a sympathectomy has been done on the arm first involved, and that arm appears normal, as normal as a sympathectomized arm will, and there is improvement in the other extremities.

I did not wish to leave the impression that complete excision of an arteriovenous aneurysm is always advisable or possible, but that many other methods, such as infolding or a transvenous closure, or some particular method devised at the moment, may be necessary in eradication of these lesions.

THE USE OF PENICILLIN IN SURGICAL INFECTIONS*†

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THE IMPORTANCE OF PENICILLIN must be gauged in accordance with its relationship to previous methods of treating infection. After eight years of experience with sulfonamide chemotherapy of bacterial infections, it is appropriate to examine the present status of these drugs as they affect the practice of surgery and to determine to what extent penicillin gives promise of meeting the limitations of the sulfonamides. Convincing evidence of the value of sulfonamide therapy is to be found in contrasting the 38 per cent-case fatality rate from meningitis during World War I with the current Army rate of 4 per cent.[1] Similar comparisons could be made with respect to pneumonia and streptococcic sepsis. However, in considering special surgical infections separately from infectious diseases as a whole, we find that the sulfonamides possess certain very definite shortcomings which are of especial significance to the surgeon. By a "surgical" infection is meant a lesion which is fundamentally associated with a localized component in soft tissue, bone, or serous cavity; within which irreversible damage to tissue architecture is likely to occur as a result of bacterial activity, and which, under certain conditions, may be benefited by surgical treatment of the localized focus. For further discussion of the special characteristics of surgical infections see Meleney.[2] Sulfonamide therapy has modified the invasive aspects of many of these surgical infections, particularly those due to hemolytic streptococci, and, in a less striking degree, to staphylococci; and has thereby reduced mortality and increased the effectiveness of associated surgical treatment; furthermore, there is reason to believe that sulfonamides have improved the prognosis of patients with various types of peritonitis of mixed bacterial flora. However, the sulfonamides have almost completely failed to influence the localized foci of tissue necrosis once they have developed, and have been least effective in surgical infections produced by those organisms which, like the *Staphylococcus aureus,* are the most active destroyers of tissue. As reported by Doctor Frank Meleney[3] before this Association a year ago, carefully controlled clinical and laboratory studies have failed to support enthusiastic claims that systemic and/or local sulfonamide therapy have modified the incidence of localized suppuration in accidental wounds of soft

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† This report is based on work done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

parts and bone, particularly if the wounds had been subjected to primary closure. In the presence of products of tissue breakdown bacteria are resistant not only to the concentrations of sulfonamides supplied in systemic therapy but are also resistant to the action of even locally applied sulfonamides. In this connection there is, as yet, little really clear-cut evidence that locally applied sulfonamides are of any practical value in the treatment of suppurating wounds (excepting only superficial lesions free of necrotic tissue) unless radical surgery is first performed, and in many such cases the surgical procedure alone might be adequate to eradicate the infection.[4]

Another factor seriously limiting the usefulness of the sulfonamides in surgical infections has been the incidence of toxic reactions, particularly those resulting from acquisition of drug hypersensitivity, and those affecting the hemopoietic system and the kidneys. These reactions have not been so frequently severe as to contraindicate sulfonamide therapy in conditions where they could be relied upon to have definite therapeutic value—but many conscientious surgeons have been reluctant to use sulfonamides in prophylaxis under conditions where the likelihood of serious infection is remote.

In view of these limitations in sulfonamide therapy as applied to surgical infections, it is only natural that the advent of penicillin as a practical therapeutic agent should have been received with interest by students in this field. Although it is not within the scope of this paper to present a complete review of the literature on penicillin, it seems desirable to present in broad outline the historical development of this remarkable drug.

It was shown by Alexander Fleming,[5] who discovered penicillin in 1929, that the drug was highly effective *in vitro* against staphylococci and other gram-positive organisms, and by Abraham, Chain, *et al.*,[6] that its activity was not seriously impaired in the presence of proteolytic products of infection. Since it is not inhibited by para aminobenzoic-acid and peptones, as the sulfonamides are, the action of penicillin appears to be different in character from that of the sulfonamides. The first reports on the administration of penicillin to patients, by the group at Oxford University led by Professor H. W. Florey, was published in 1941.[6] Although they were working with rather small amounts of the drug, their results in severe staphylococcic infections were definitely encouraging and lent justification to energetic efforts to increase the production of penicillin both in England and the United States. The large-scale production of the drug, derived from cultures of a certain strain of the mold *Penicillium notatum*, presented technical problems of an unprecedented nature, but as a result of the cooperative efforts of the British Medical Research Council, the Committee on Medical Research, the War Production Board, and several pharmaceutical houses both in Britain and the United States, and the laboratories of the U. S. Department of Agriculture in Peoria, Illinois, these problems have been successfully overcome, and the production of penicillin has now reached such a volume as to permit ample supplies for laboratory and clinical research. During the past fourteen months the Committee on Chemotherapeutics and Other Agents of the

National Research Council, acting for the Committee on Medical Research, has been responsible for the planning and execution of clinical research on penicillin, using supplies of the drug purchased from the manufacturers by the Office of Scientific Research and Development and allocated for civilian use by the War Production Board. As Chairman of this Committee, Doctor Chester S. Keefer has met urgent requests from civilian physicians for penicillin in treatment of severe sulfonamide-resistant infections in which penicillin therapy might be indicated.

For special research on surgical infections, penicillin has been provided to investigators working under the program of the Subcommittee on Infected Wounds and Burns, of the National Research Council, and to the Army and Navy. It is the purpose of this paper to present in rather general terms what has been learned by one of the participating groups regarding the scope and limitations of penicillin in surgical infections and to bring out the extent to which penicillin gives promise of meeting some important deficiencies of the sulfonamides through its effectiveness in the presence of pus, its powerful action against staphylococci, and its lack of toxicity. Among the few papers which have already been published on this subject is the significant report of Major Champ Lyons[7] on experience with penicillin in Army hospitals. Reports of general clinical studies on penicillin have been published by a number of investigators, including Abraham, Chain, Fletcher, Gardner, Heatley, Jennings and Florey,[6] Keefer, Blake, Marshall, Lockwood and Wood,[8] Dawson and Hobby,[9] Herrell,[10] and Bloomfield, Rantz and Kirby.[11]

TABLE I

PENICILLIN-SUSCEPTIBLE	
Gonococcus	*Staph. aureus*
Meningococcus	*Staph. albus*
Str. hemolyticus	*Cl. tetani*
Str. viridans	*Cl. welchii*
Actinomyces bovis	*Cl. diphtheriae*
PENICILLIN-RESISTANT	
Enterococcus	*B. pestis*
Esch. coli	*B. proteus*
B. typhosus	*B. pyocyaneus*
B. paratyphosus	*B. Friedländer*
B. dysenteriae	*Brucella*
H. influenzae	*B. tuberculosis*
H. pertussis	*B. tularensis*

PROPERTIES OF PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

Penicillin comes from the manufacturer in the form of the anhydrous sodium or calcium salt, varying in color from light yellow to deep reddish-brown. It is highly soluble in water, but tends to deteriorate in solution, particularly at room temperature or higher. In the anhydrous state it is fairly stable, and may be kept for several months without deterioration, particularly at refrigerator temperature. It is highly active *in vitro* against most gram-positive species of bacteria, including *Staphylococcus aureus* and *albus, Streptococcus hemolyticus,* and the *Clostridia,* and is also active against

the gonococcus and the meningococcus. The unit of penicillin is based on its activity *in vitro* and consists in the amount of the drug which must be added to 50 cc. of broth in order to prevent the growth of a standard strain of *Staphylococcus aureus*. Therefore, one milligram of commercial penicillin, which contains on the average about 500 units of activity, would inhibit the growth of *Staphylococcus aureus* in 25 liters of culture media. Penicillin is not active against most types of gram-negative bacilli, including *Esch. coli, B. pyocyaneus* and *B. proteus;* in fact the colon bacillus produces a substance, penicillinase,[12] which will rapidly destroy the activity of penicillin—a phenomenon of considerable importance in the practical treatment of surgical infections where this organism is present in mixed culture with gram-positive, susceptible organisms.

The mode of action of penicillin is still unknown. Strictly speaking, it is a bacteriostatic drug in that it apparently produces its effect on bacteria in the host by destroying their ability to multiply; once bacteria in the body cease to multiply and produce toxins they are rapidly destroyed by the antibacterial mechanisms of the host. Since the concentration required for this action is exceedingly small, about one-thousandth of a milligram of the pure drug per 100 cc. of media, it is reasonable to believe that penicillin must exercise a highly selective effect on an enzyme system concerned in the process of bacterial growth. Its usefulness as a chemotherapeutic agent is a result of its ability to circulate throughout the body fluids in an active state and without producing any apparent toxic action on the cells of the host.

Penicillin must be administered parenterally, because it is inactivated by gastric juice and is not readily absorbed from the intestinal tract. It is rapidly excreted in the urine and in the bile, the rate of its excretion and the concentration in the blood depending upon the route of injection.[13] The highest blood concentrations and excretion rates occur with intravenous injection and the lowest with subcutaneous administration while the curves for intramuscular injections occupy an intermediate position. In practice, penicillin is usually given either by continuous intravenous drip, the 24-hour dose of drug being dissolved in the amount of normal saline or glucose which the patient can be given intravenously during this period, or in repeated intramuscular injections at intervals of two, three, or four hours, depending upon the intensiveness of treatment required. At this period in the development of penicillin, when the supply is limited, it is perhaps fortunate that the drug must be given parenterally, and, therefore, usually in hospitals, because, apart from existing legal restrictions, this provides the only effective brake on the indiscriminate use of penicillin for all sorts of minor conditions.

The dosage of penicillin in various types of infections is not yet standardized. Emphasis has necessarily been placed upon determination of minimal effective doses for different types of infections because of the scarcity of the drug, but the almost complete lack of toxicity of penicillin has permitted considerable latitude in pushing dosage upward when smaller doses are ineffective. Most cases of gonorrhea will, for example, respond to

10,000 units every three hours for five doses, a total of 50,000 units. However, in cases of severe staphylococcic bacteremia, the average dose of 120,000 units per day for ten days may at times be increased to 300,000 or 400,000 units per day for a similar period. Increasing systemic dosage beyond this point will probably result only in waste of the drug. Duration of treatment, of course, depends upon the clinical response of the individual case, upon the timing and feasibility of associated surgical procedures designed to remove penicillin-resistant foci such as bone sequestra, and, finally, upon clinical judgment in respect to the likelihood of relapse in the type of infection being treated. Much more experience will be required before definitive rules can be provided in these matters of dosage and duration of treatment.[7]

LOCAL USE OF PENICILLIN

There are a number of conditions in which it appears to be desirable to use local penicillin either in conjunction with systemic therapy or by itself. It happens that penicillin is not readily permeable through serous and endothelial membranes, including the so-called "blood-brain barrier," therefore, it is usual practice in treatment of meningitis to inject about 10,000 units once or twice daily into the lumbar canal or the cisterna. In a similar way penicillin may be injected into empyema cavities and infected joints into which the passage of penicillin from the blood is usually quite limited; the high local concentrations produced by this method probably aid in causing disappearance of the infecting organisms, but will not necessarily render surgical drainage unnecessary in chronic cases if the cavity is thick-walled and contains large masses of heavily infected fibrin. Penicillin solutions containing 50 to 250 units per cc. may be used for semi-continuous irrigation of contaminated or infected wounds and are especially useful, in our experience, in the postoperative management of wounds incident to sequestrectomies for chronic osteomyelitis.

Studies now in progress under the auspices of the Committee on Medical Research should develop the possibilities of penicillin in various vehicles for local treatment of wounds; as yet, our own clinical experience with these preparations has been inadequate to justify any definite statements other than that the results are highly encouraging. However, Florey and Williams[14] have reported a controlled series of 110 minor surgical infections of the hand in which the results of local penicillin treatment as an adjunct to surgical therapy were compared with 102 control cases treated by standard methods. Among 35 pulp and tendon sheath infections, alone, the saving of working time attributable to penicillin was 1000 days! "In the penicillin treated series, given adequate access and removal of dead tissue, sepsis by clinical and bacteriologic criteria was eliminated within a week." The total amount of penicillin used to treat over 100 cases locally was less than 500,000 units, which is a minimal dosage for *systemic* treatment of one case of severe sepsis. Another group[15] in Britain have found an ointment containing penicillin to be useful in shortening the healing time of infected superficial

burns. Garrod[16] has written on the prophylaxis and treatment of war wounds with penicillin.

LABORATORY STUDIES

One fact which has stood out as of paramount importance in the effective utilization of penicillin has been the necessity for careful bacteriologic study of every case in which the drug is used. In the first place, one must know whether or not the causative organism is susceptible, because occasional resistant strains of staphylococci or streptococci are encountered which will require more intensive treatment. Determination of sensitivity of an organism to penicillin can be performed by a simple procedure adaptable to any bacteriology laboratory.[6] In the second place, it is important to identify the presence of penicillin-resistant species such as *Esch. coli,* or *B. pyocyaneus* or *B. proteus;* although not highly parasitic in wounds when in pure culture, these types of bacteria are not only resistant to ordinary concentrations of penicillin but as previously mentioned, some of them elaborate a "penicillinase" which rapidly destroys penicillin and may interfere with the action of the drug on penicillin-susceptible species which are present in the wound. Finally, frequent examination of the bacterial flora of the exudate in a localized infection, or the blood in a case of bacteriemia, is the best method of determining the adequacy of treatment in any individual patient, and may be employed in determining the optimal time for surgical intervention in cases of chronic osteomyelitis with draining sinuses or in determining a favorable time for secondary suture.

Determination of the concentration of penicillin in the blood and body fluids is a procedure requiring some special laboratory facilities and technical skill,[17] and, though important to the conduct of research on penicillin, will probably not be essential to the routine practical use of the drug in treatment of infections. In this respect penicillin differs greatly from sulfonamides because excessive blood levels of penicillin are simply wasteful and not actually dangerous to the patient. Determination of susceptibility of the organism to penicillin and of the clinical and bacteriologic response of the patient are adequate practical guides to the administration of this drug. It goes without saying that in using penicillin in the treatment of acute and chronic infections one must not lose sight of the importance of other aspects of therapy, such as maintenance of adequate nutrition, correction of anemia of the results of many investigators will be of far greater significance than ment of wounds. These considerations have been well emphasized by Lyons.[7]

RESULTS OF PENICILLIN IN SURGICAL INFECTIONS

During the past 18 months our penicillin research unit at the University of Pennsylvania has been privileged to treat about 440 patients, not only in our own hospitals, but also in many other institutions in Philadelphia. In some of these cases the entire clinical management has been in our hands, but in many we have served only as a distributing agency for supplying the

drug after having satisfied ourselves as to the suitability of the case for penicillin treatment. In all cases the opportunity has been given to us of regulating dosage and laboratory studies, making frequent examination of the patients, and preparing special research records. The diseases treated have been of many varieties—both medical and surgical, and except for special research cases of chronic osteomyelitis and pulmonary suppuration, all of them were critically ill. Most of them had received intensive sulfonamide treatment without success for periods of two days to several weeks. As a rule, the request for penicillin was not made by the attending surgeon or physician until other available measures had failed to effect a cure, and, with only limited amounts of penicillin available, we were disposed to treat only such cases as had failed to respond to other therapeutic measures. This has made it possible for us to study severe infections in all stages of development, from very early lesions to very advanced ones. Because of the wide scope of this study we have chosen to avoid any attempt at a presentation of our detailed statistics at this time. The statistics to be published later through a pooling of the results of many investigators will be of far greater significance than those from any one unit. Instead, we propose in this paper to discuss in a general way, the results of penicillin therapy in several broad categories of surgical infections—introducing selected case summaries to illustrate the bases for the conclusions which we feel permitted to make. The four main groups to be discussed are acute disseminated sepsis, and localized infections of serous cavities, soft tissues, and bone, respectively.

ACUTE DISSEMINATED SEPSIS (BACTERIA AND MENINGITIS)

Included in this group were 57 cases of staphylococcic bacteriemia of which two-thirds survived; 15 cases of streptococcic bacteriemia and 50 cases of suppurative meningitis, of which 43 were pneumococcic and 5 staphylococcic. The cases of staphylococcic bacteriemia probably illustrate better than any others the important position of penicillin as a chemotherapeutic agent. Whenever possible these cases were treated by the continuous intravenous drip method and received doses of 60,000 units to 150,000 units in each 24-hour period. With impressive regularity these patients tended to show improvement within 48 hours and, unless complications had developed, were clinically recovered from the acute disease within three to seven days. The complication most likely to interfere with successful treatment was vegetative endocarditis, which developed in ten cases. In most of these bacteriemia cases no resort was made to surgical treatment of foci of localization during the acute septic phase of the infection because in the face of progressive improvement in the patient's condition it seemed wise to defer operative procedures until a time of election. In several instances the foci of localization subsided without requiring drainage, particularly those developing in well vascularized tissues about the face, and in the lung. When localization in bone occurred it has usually been necessary to resort, ultimately, to surgical drainage. This will be discussed later as a special topic.

Case 1.—H. E. (Fig. 1): *Diagnosis:* Cavernous sinus thrombosis. *Staphylococcus aureus* bacteriemia.

A 35-year-old Negro developed swelling of eyelids and fever two days following a severe blow on the nose. On admission to the Pennsylvania Hospital, March 6, 1943, he was acutely ill, showed chemosis and proptosis, with engorgement of veins and ophthalmoplegia on the left side. Blood culture was positive for *hemolytic Staphylococcus aureus.* The same organism was present in purulent drainage from the right eye. After failure to respond to sulfadiazine for 48 hours he was given penicillin intravenously. Heparin and dicoumarin were given to prevent propagation of thrombi. His response to the treatment was very satisfactory. Temperature became normal in four days. The local signs subsided progressively. He was discharged, well, on April 25, 1943.

Case 2.—B. C. (Fig. 2): *Diagnosis: Staphylococcus aureus* bacteriemia; questionable acute endocarditis.

An 11-year-old boy entered the Hospital of the University of Pennsylvania, May 26, 1943, during the third week of an acute illness characterized by fever of 104° to

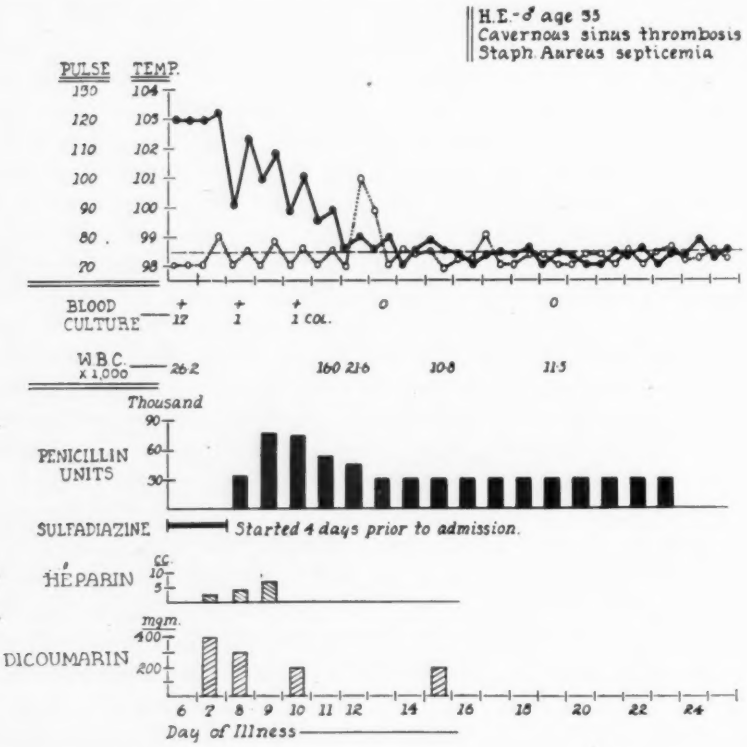

Fig. 1.

106° F., headache, and delirium. He had received sulfathiazole and sulfadiazine without apparent benefit. The day before admission petechiae had appeared on the extremities, and soon appeared in conjunctivae and mucous membranes as well. Blood culture was positive for *hemolytic Staphylococcus aureus.* Penicillin was started by intravenous drip in doses of 100,000 units daily. Blood culture remained positive for two days, spleen became palpable and tender, and a rough systolic murmur appeared, justifying a diagnosis of acute vegetative endocarditis. Spiking fever continued in spite of the

development of negative blood cultures. On June 6, when the temperature reached 106° F., it was decided in desperation to try combining sulfadiazine with penicillin. Prompt and progressive improvement followed. Within a week the temperature had reached near-normal levels, the heart murmur disappeared, and the patient appeared to be convalescing. There were some febrile episodes in his course thereafter, the most alarming being associated with unexplained meningismus and pleocytosis of the

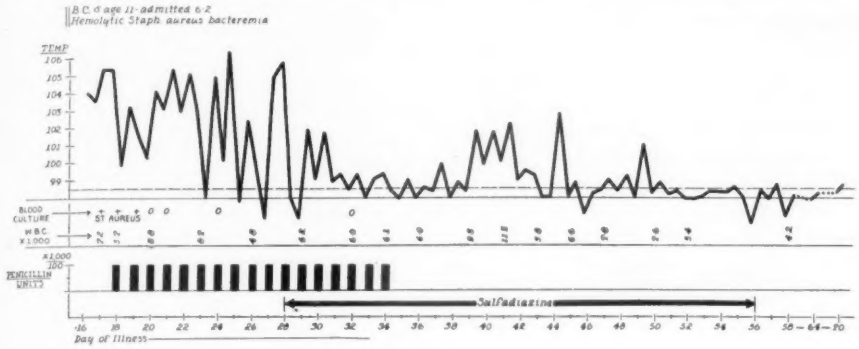

Fig. 2.

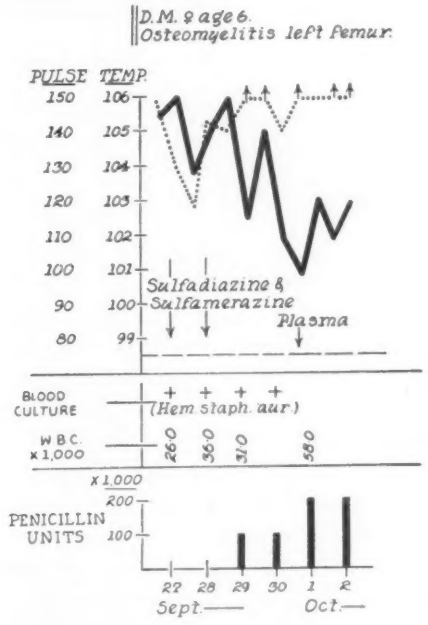

Fig. 3.

cerebrospinal fluid, but there was no recurrence of staphylococcic sepsis. He was finally discharged in good condition on July 18. At no time did he develop any lesions requiring surgical drainage. The primary focus of his infection remained indeterminate.

This case apparently represents a recovery from acute staphylococcic endocarditis, a complication which has seemed usually to be fatal in spite of penicillin. The clinical

evidence of the value of combined therapy with sulfonamides and penicillin tends to confirm laboratory studies on this point.

Case 3.—D. M. (Fig. 3): *Diagnosis: Staphylococcus aureus* bacteriemia and meningitis.

A six-year-old white girl came into the Jewish Hospital, September 27, 1943, three days after acute onset of pain in the left hip and thigh. Her temperature was fluctuating between 105° and 107° F. A diagnosis was made of acute osteomyelitis of the left femur, with *Staphylococcus aureus* bacteriemia. Petechiae appeared, but without other evidence of endocarditis. Penicillin was commenced on September 29, 1943, and continued for two days at 100,000 units per day, and for one day at 200,000 units. In spite of these doses, which were large for a child of her age, the bacteriemia persisted, she showed no evidence of response to treatment and died October 2, 1943.

Autopsy disclosed widespread staphylococcus infection involving meninges, lungs, kidneys, left femur and left knee joint. Laboratory studies revealed that the inhibiting concentration of penicillin for this organism was *four hundred times* the usual level for *Staphylococcus aureus*. This fact explained the fatal outcome.

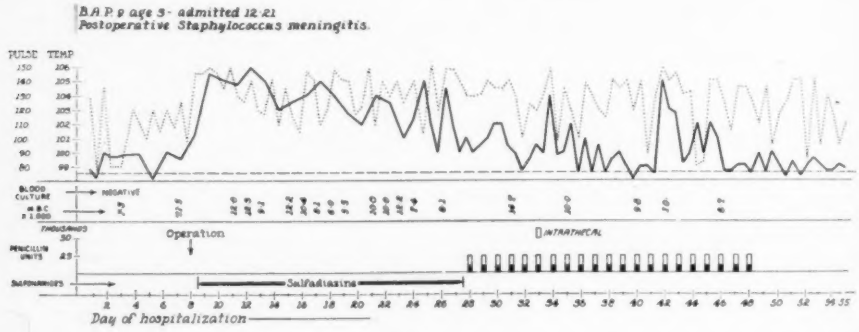

Fig. 4

Meningitis, with or without bacteriemia, has continued to present major problems in management. Some of the cases, particularly those due to staphylococci, have responded rather promptly, even at times without intrathecal treatment, but the patients with pneumococcic infection have, in our experience, required especially energetic treatment, and the majority have died, nevertheless. As a rule, it was possible to obtain a marked bacteriologic response in these cases, the blood stream and spinal fluid showing either marked reduction in numbers of bacteria or even frank sterilization, but with the patient then succumbing either to hydrocephalus from mechanical block of spinal fluid drainage, from an acute toxic encephalitis, or from bacterial endocarditis. In cases of pneumococcic meningitis we feel that a daily injection of about 10,000 units of penicillin into the lumbar canal, cistern, or ventricles is imperative—and recent experiences suggest that the cisterna injections are particularly advantageous in severe infections. In meningitis it remains a matter of great importance to explore potentially infected mastoids in cases where a prompt clinical response is not forthcoming.

Case 4.—B. A. P. (Fig. 4): *Diagnosis:* Postoperative *Staphylococcus aureus* meningitis.

Following operation, December 28, 1943, for cerebellar tumor this three-year-old child developed an acute *Staphylococcus aureus* meningitis. Treatment for 18 days with sulfadiazine failed to relieve the infection and spinal fluid cultures remained positive. Penicillin was started systemically and intrathecally on the 19th day and continued for three weeks. Spinal fluid cultures became negative after the first day of treatment and remained so thereafter. One week after completion of penicillin treatment she was discharged in good condition.

Case 5.—D. K. (Fig. 5): *Diagnosis:* Pneumococcic meningitis following mastoiditis.

This two and one-half-year-old baby was admitted to the service of Dr. William Atlee, Lancaster, Penna. General Hospital, February 9, 1944. He was acutely ill and stuporous with pneumococcic (Type XIV) meningitis secondary to acute otitis and mastoiditis. During the first four days sulfadiazine and specific antiserum were admin-

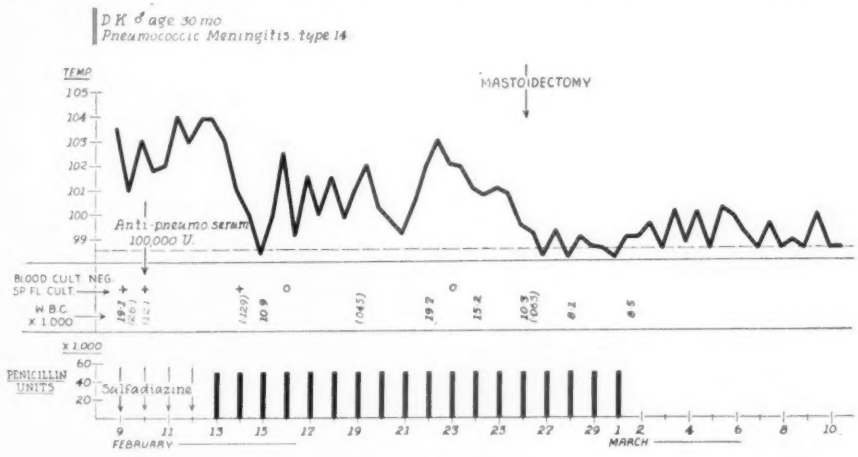

Fig. 5.

istered, without improvement; stupor remained and right hemiplegia and nystagmus appeared. Penicillin in doses of 50,000 units daily intramuscularly was started on February 13, and 5,000 units were given daily into the cisterna. Within four days marked improvement had occurred. Negative cultures of spinal fluid were obtained on February 16. The temperature rose again on the 22nd and 23rd, when penicillin was given by lumbar, instead of cisterna, puncture, but spinal fluid culture remained negative. On February 26 a radical mastoidectomy was performed. Five days later the penicillin was stopped. The mastoid wound healed uneventfully. He gradually recovered from the paralysis, and by March 24 was able to walk.

This case represents a recovery from meningitis of extreme severity. It illustrates the importance of intrathecal penicillin, the possible superiority of cisternal lumbar injections, and the need for surgical drainage of primary foci.

Of the 44 cases of pneumococcic meningitis which we have treated only eleven have recovered, and three of these are hopeless "spastics." All of the five cases of staphylococcic meningitis recovered. It is probable that through increasing experience with the use of penicillin in these cases, and

with more frequent employment of intracisternal treatment, recovery in a considerably larger proportion of patients with this disease may be obtained. Penicillin is quite adequate to deal with the pneumococcus when intimate contact of bacteria and drug can be effected.

LOCALIZED INFECTIONS IN SEROUS CAVITIES

A. *Empyema:* When the empyema is due to an infection with a penicillin-sensitive pneumococcus, staphylococcus, or streptococcus, in pure culture, and treatment is instituted within the first few weeks, it is possible to bring

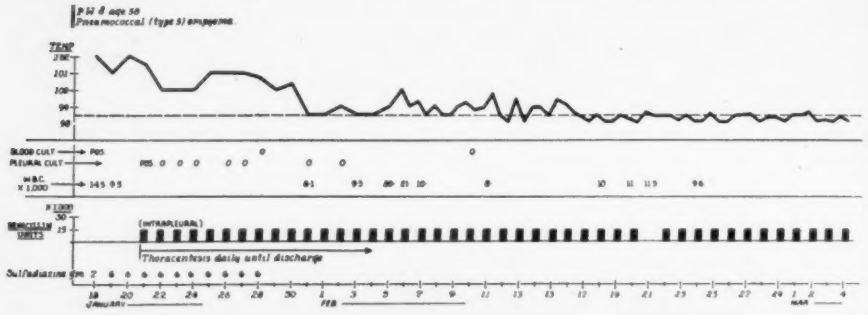

Fig. 6.

(a) (b)

Fig. 7.—P. W. Pneumococcal (type 5) Empyema. (a) X-ray on admission to hospital. (b) X-ray 13 days after penicillin treatment was started.

about sterilization of the cavity, and ultimate cure, without resorting to thoracotomy drainage. We have seen this accomplished in 19 cases through frequent aspiration of the cavity and injection of 10,000 to 25,000 units of the drug. If the patient is acutely ill, or shows other evidence of continuing parenchymal infection in the lung it is necessary to use systemic treatment in combination with the local injections. Failure to obtain a satisfactory bacteriologic and clinical response after two or three weeks of treatment will, of course, demand a resort to rib resection, but convalescence is shortened when this can be avoided.

Case 6.—P. W. (Figs. 6, 7 and 8): *Diagnosis:* Pneumococcic empyema.

This 58-year-old, white male, entered the Jefferson Hospital, January 18, 1944, on the fifth day of an attack of pneumococcic lobar pneumonia. Blood culture was positive

(a) (b)

FIG. 8.—P. W. Pneumococcal (type 5) Empyema. (a) X-ray 26 days after penicillin treatment was started. (b) X-ray 1 month after discharge.

for Type V pneumococcus. He received sulfadiazine from admission until January 29. Aspiration of the chest on January 20 revealed thick, green pus; culture again showed Type V pneumococcus. The patient was treated with daily aspirations of pus and injection of 18,000 units of penicillin from January 21 to March 4. Cultures of the

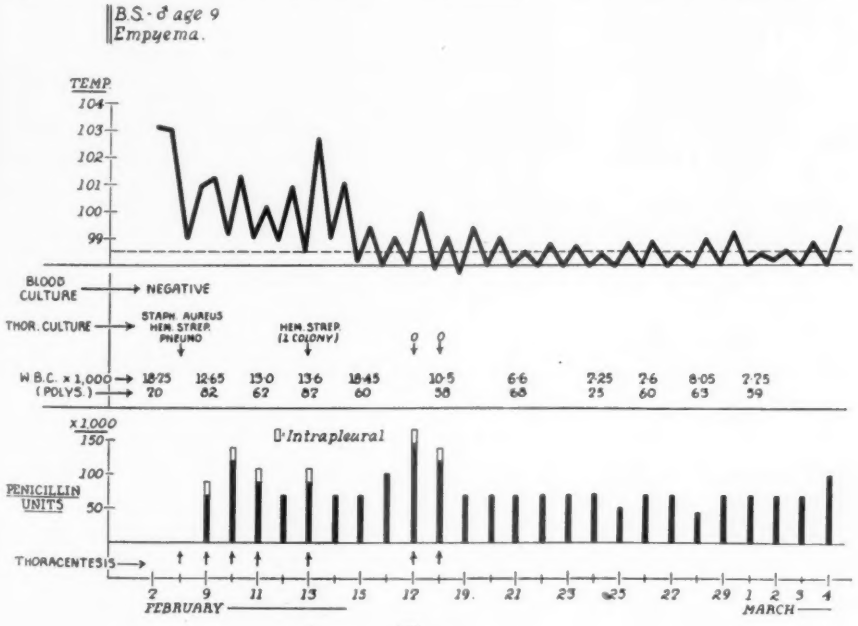

Fig. 9.

empyema fluid were negative after the first injection of penicillin and remained so thereafter except for one positive culture on January 31. He was discharged, March 4, 1944, and has remained well subsequently.

Case 7.—B. S. (Figs. 9, 10, 11, 12 and 13): *Diagnosis:* Empyema, polymicrobic.

This nine-year-old boy entered the Woman's Medical College Hospital, February 7, 1944, because of empyema which had developed following pneumonia treated with sulfadiazine five weeks before. Aspiration on February 8, 1944, showed 50 cc. of thick creamy pus, containing *Staphylococcus aureus*, *Streptococcus hemolyticus* and *Pneumococcus*. Penicillin was given systemically from February 9 to March 4, a total of 1,875,000 units. In addition, aspiration of pus and injection of 20,000 units of penicillin was performed on six occasions between February 9 and February 18. The culture on February 13, after four days of penicillin, showed only one colony of hemolytic

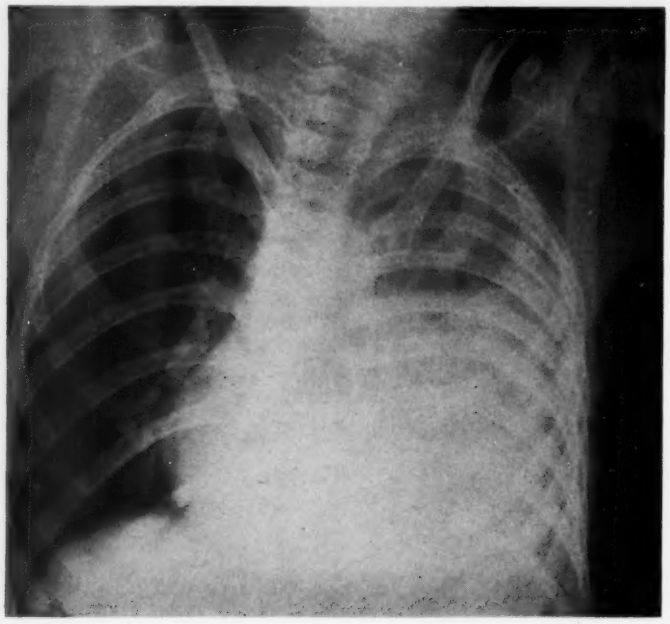

FIG. 10.—B. B. Empyema—X-ray of chest 2nd day of penicillin treatment.

streptococcus, and subsequent cultures were sterile. The child's condition showed a parallel improvement, and by March 3 the empyema cavity was completely obliterated. He was discharged March 10, 1944, with evidence of slight pleural thickening, but otherwise in good condition.

This presents a good response in a mixed infection, but all of the organisms were sensitive to penicillin.

It should be observed that almost all current cases of empyema have had sulfonamide therapy, which has certainly modified the severity of the disease, and even brought about cure in many early cases, without need for surgical drainage. From our experience in the 34 cases of pneumococcic empyema, we are inclined to feel that treatment according to the plan carried out in the above case, without systemic penicillin, will permit avoidance of surgical drainage in perhaps the majority of cases when the empyema is unilocular. A single daily injection is sufficient to maintain a high concentration of penicillin in the pleural cavity. Of course, this treatment will be ineffective when the cavity is multilocular unless each pocket is dealt with separately.

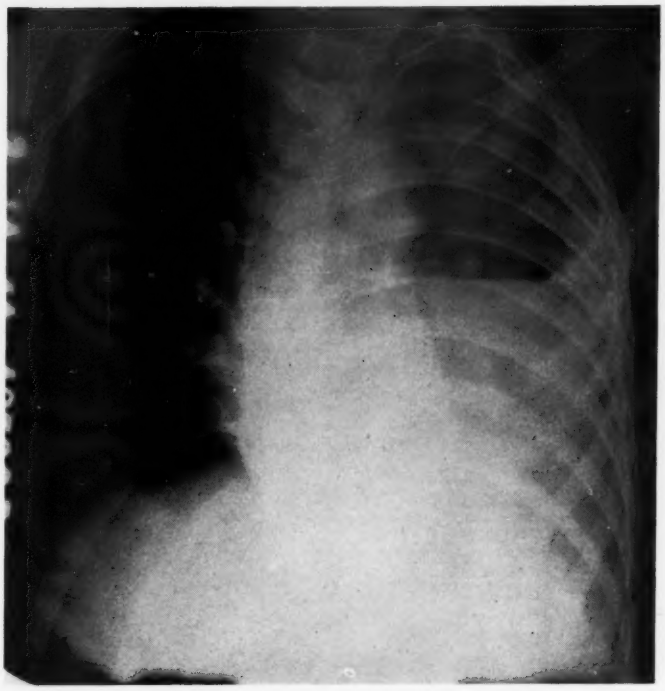

FIG. 11.—B. B. Empyema—X-ray of chest 6th day of penicillin treatment.

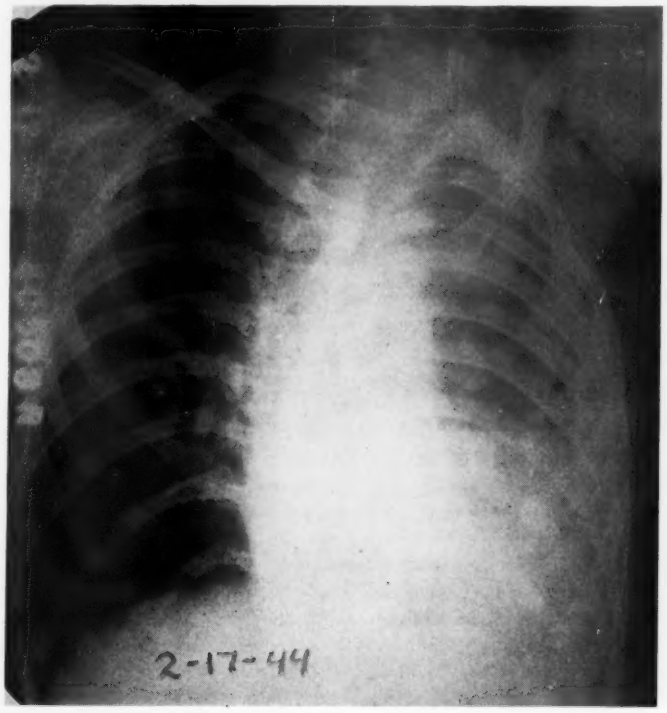

FIG. 12.—B. B. Empyema—X-ray of chest 9th day of penicillin treatment.

B. *Suppurative Arthritis:* What has been said in regard to empyema tends also to apply to suppurative arthritis. Complete restoration of function after staphylococcic arthritis has occurred in several cases.

Case 8.—E. R.: *Diagnosis:* Arthritis of knee due to *Staphylococcus aureus.*

A 33-year-old male came in for treatment of a chronic infection of the right suprapatellar bursa and knee joint. He had had an amputation of his left leg seven years before because of recurrent osteomyelitis. The present lesion was associated with a persistent infection in the lower end of the right femur which had been draining

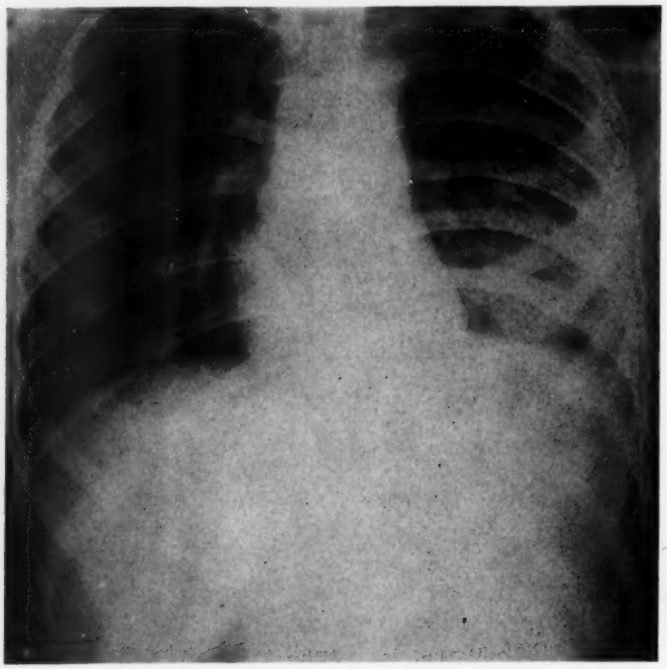

FIG. 13.—B. B. Empyema—Follow-up X-ray 2 weeks after discharge.

almost continuously for two and one-half years. At the time of an episode of active infection in June, 1943, the right knee joint had become infected with frank pus, and the surgeon who was taking care of him at that time inserted through-and-through drainage with rubber dam across the suprapatellar bursa. When he entered the Hospital of the University of Pennsylvania, November 17, 1943, he had been carrying this drain through his knee joint for more than four months. The infection in the femur was quiescent, but large quantities of pus were pouring from the drainage wounds of the joint. Culture showed *hemolytic Staphylococcus aureus* and diphtheroids. Penicillin, 100,000 units per day intramuscularly, was started on November 18 and continued until November 27, by which time drainage had practically ceased and culture showed only diphtheroids. On that day he was operated upon—the scarred sinuses were excised down to the thickened synovia and two small catheters were introduced. Systemic penicillin was continued and, in addition, 1,800 units of dilute penicillin was injected through the catheters every six hours. After one week, the cultures having remained sterile, the catheters were removed and two days later the systemic drug was discontinued. Active motion of the joint was then commenced. Infection did not recur, though straw-colored fluid free of staphylococci continued to drain intermittently for

several weeks. By February 1, 1944, his wounds were entirely healed. He was reexamined March 3, 1944, when his knee showed full range of motion. He is now back at regular work, entirely free of symptoms.

This case illustrates the remarkable recuperative power of chronically infected synovial tissue when active infection is eliminated with penicillin.

Case 9.—H. S.: *Diagnosis:* Suppurative arthritis of ankle due to *Staphylococcus aureus.*

A 64-year-old white male developed a suppurative arthritis of the ankle and was admitted to the Pennsylvania Hospital, April 14, 1943, the fifth day of disease. He showed only moderate systemic reaction but aspirated joint fluid showed pure culture of *Staphylococcus aureus.* The culture remained positive after four days of sulfadiazine therapy. Penicillin was given in doses of 100,000 units daily for one week, and at 50,000 units daily for nine additional days. On the fourth day of penicillin treatment, the joint fluid became sterile and remained so. After a period of treatment of careous teeth he was discharged with a normally functioning ankle joint on June 18, 1943.

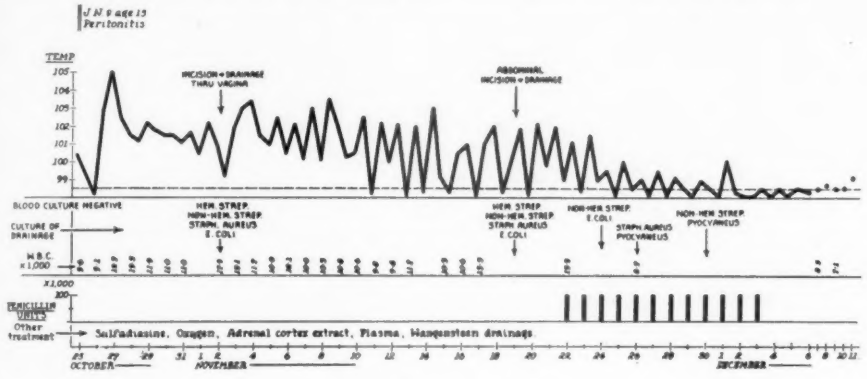

Fig. 14.

It is worthy of note that this patient received no local treatment of the infected joint other than aspiration. He would probably have recovered more rapidly if penicillin had been administered by injection into the joint.

C. *Peritonitis:* It has been possible to study only a few cases of peritonitis —partly because the limited supply of the drug has been inconsistent with treatment of infections in which penicillin-resistant organisms predominate, and partly because of the difficulty of evaluating the influence of a chemotherapeutic agent in lesions where there is considerable likelihood of recovery without the drug. Certainly, the cases of primary peritonitis from hemolytic streptococcic or pneumococcic infection would be expected to respond favorably to penicillin treatment. Less certain would be the results in treatment of infection developing after appendicitis, including pylephlebitis and perihepatic infections. However, some encouragement is to be found in cases such as the following:

Case 10.—J. N. (Fig. 14): *Diagnosis:* Diffuse peritonitis, polymicrobic.

This 15-year-old girl came in in shock and with paralytic ileus from appendical peritonitis which appeared clinically to be of generalized extent. She was given sulfadiazine,

plasma, Wangensteen suction, and oxygen. After a stormy week she developed a pelvic abscess which pointed in the vagina and was drained. Some improvement followed, including return of peristalsis, but elevated temperature, pulse and respirations persisted and her condition appeared critical. Blood cultures were negative. Another abscess was drained through a McBurney incision, November 19, 1943, but no improvement resulted. The pus from both abscesses showed hemolytic and nonhemolytic streptococci, *Staphylococcus aureus* and *E. coli*, and the second abscess showed *Cl. welchii* in addition. On November 22 penicillin in daily dose of 120,000 units was started intramuscularly at two-hour intervals. On November 24 her temperature remained for the first time at near normal levels and she began to feel much better. Culture showed disappearance of hemolytic streptococci. By November 26 only the nonhemolytic streptococci were present in the wound. Penicillin was continued until December 4, until normal temperature had remained for one week. She was discharged on December 12, but returned for uncomplicated appendicectomy in March, 1944.

In this case it appeared that the severity of the illness was attributable to hemolytic streptococcic infection. Once this organism was eliminated with penicillin she improved very rapidly.

Case 11.—E. B. (Fig. 15): *Diagnosis:* Acute suppurative pancreatitis.

After severe upper abdominal pain and nausea of eight days duration, t..is 33-year-old white female showed a sharp rise of temperature to 105° F., W.B.C. of 33,000, and

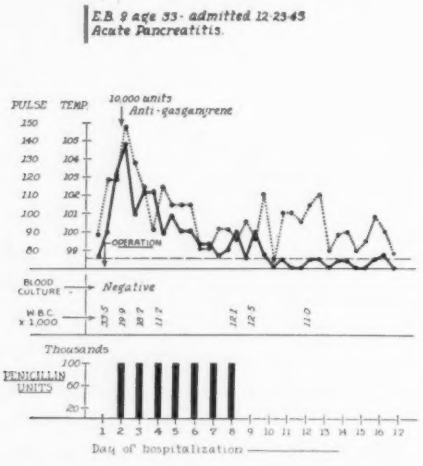

Fig. 15.

was operated upon for acute pancreatitis. Culture of the inflamed pancreas showed *Cl. welchii* and *hemolytic Staphylococcus aureus.* Cholecystostomy and drainage of the pancreas were performed by Dr. J. E. Rhoads. The following day, when bacteriologic report was available, she was given 10,000 units of polyvalent antigas gangrene serum and started on 100,000 units of penicillin per day by continuous intravenous infusion. Rapid and progressive improvement followed, as shown in the chart, and she was discharged on the 16th day.

Certainly, there would be no justification for suggesting any modification in the indications for surgical intervention in cases of appendicitis, cholecystitis and peritonitis. Good results should be hoped for only in occasional cases

selected for penicillin treatment on the basis of careful bacteriologic examination.

LOCALIZED INFECTIONS IN SOFT TISSUES

A. *Cellulitis of the Face and Orbit:* Particularly striking have been the results of treatment in patients with cellulitis of the face and periorbital tissues. The recuperative power of these well vascularized areas is illus-

FIG. 16.—A. M. S. Orbital cellulitis.

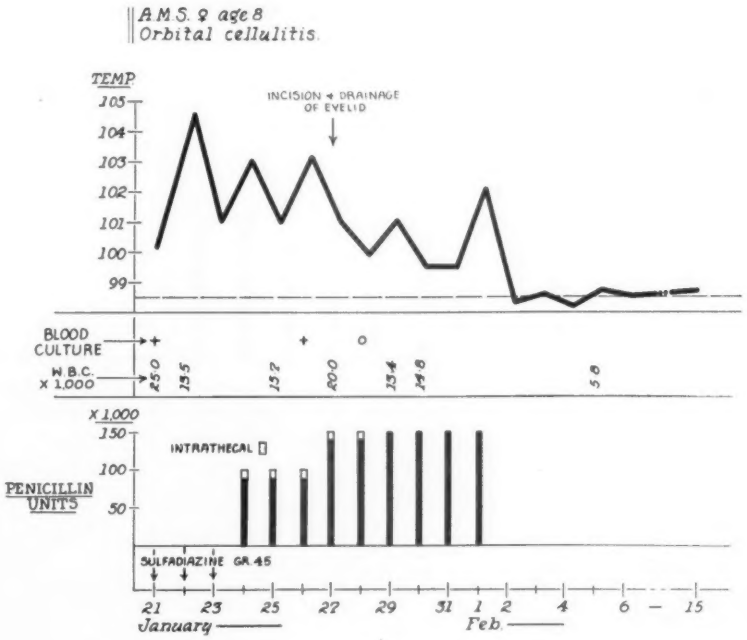

Fig. 17.

trated by the frequency with which penicillin treatment has been sufficiently effective to prevent suppuration in areas of facial cellulitis. (Refer to Case 1.)

Case 12.—A. S. (Figs. 16 and 17) : *Diagnosis:* Orbital cellulitis.

This eight-year-old girl developed furunculosis of the right lower eyelid, and was admitted in stuporous condition to the service of Dr. William Atlee, St. Joseph's Hospital, Lancaster, Pa., January 21, 1944. In spite of sulfadiazine she developed bronchopneumonia and meningitis, but with sterile cultures. On January 24 the blood culture showed *Staphylococcus citreus* and there was evidence of spreading infection. Penicillin was started intravenously at 100,000 units per day, and 10,000 units were administered daily by lumbar puncture. After two days the dose of systemic penicillin was increased to 150,000 units because the blood culture was still positive. By January 27 the lesion of the right eyelid had localized sufficiently to permit incision and drainage. Culture showed *Staphylococcus albus.* At the same time the ethmoid plate was curetted and

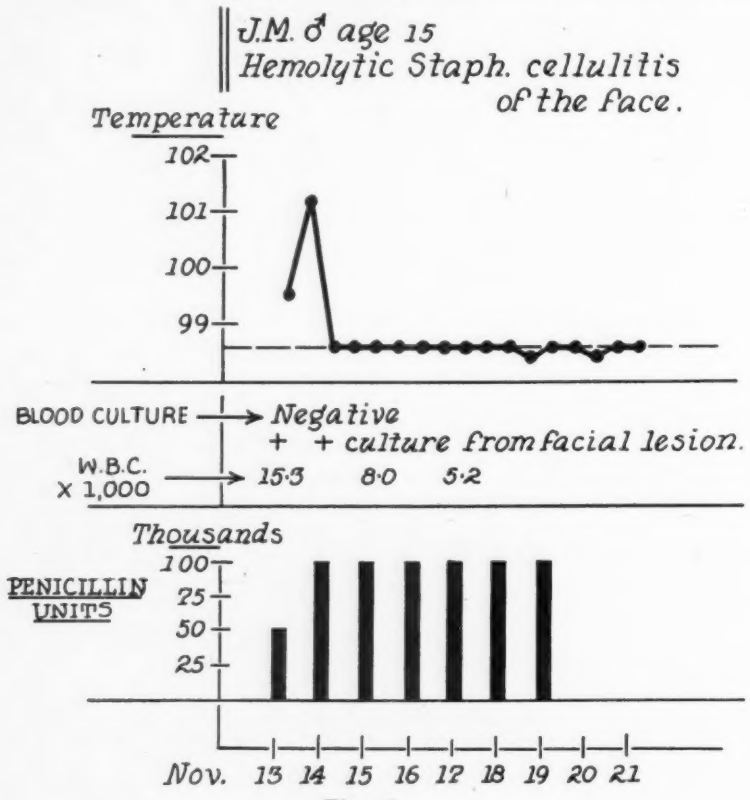

Fig. 18.

found to be infected. Her subsequent recovery was uneventful. Penicillin was discontinued on February 1, and she went home two weeks later with the drainage wound of the eye completely healed.

Case 13.—J. M. (Fig. 18) : *Diagnosis:* Cellulitis of the face, *Staphylococcus aureus.*

A 15-year-old school boy developed cellulitis of the upper lip following severe trauma, and was admitted to the Hospital of the University of Pennsylvania, November 13, 1943, under care of Dr. T. Grier Miller. The entire right cheek was involved and both eyelids were swollen. Culture of the lip wound showed *hemolytic Staphylococcus aureus.* After 24 hours of penicillin, at 100,000 units per day, his temperature became normal. Regression of the cellulitis took place rapidly, and the patient was discharged on the tenth day, with his wound healed.

In this case the development of serious complications was prevented by prompt use of penicillin.

Case 14.—D. B. (Fig. 19): *Diagnosis:* Orbital cellulitis—bacteriemia due to nonhemolytic streptococcus.

On March 23, 1943, the Army Station Hospital in Atlantic City admitted an 18-year-old Air Force cadet who had developed severe pansinusitis following measles, and

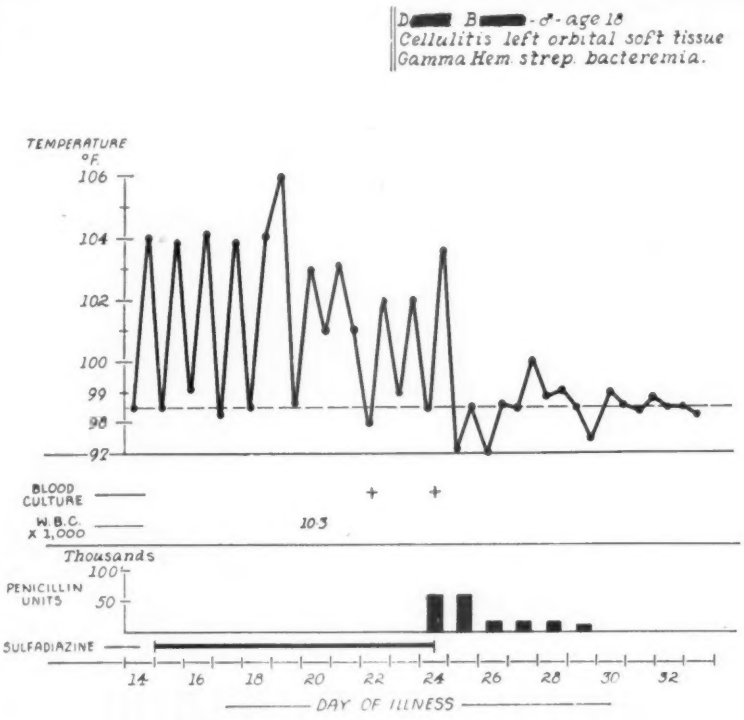

Fig. 19.

had been placed on sulfadiazine therapy. When a "picket-fence" temperature curve developed, two blood cultures revealed nonhemolytic streptococcus bacteriemia, and he began to show signs of orbital cellulitis, with proptosis and chemosis of his right eye. On April 10, 1943, penicilllin was commenced in doses of 120,000 units per day. Rapid improvement followed, the temperature falling from 103° F. to normal within 12 hours, and it remained normal thereafter. Subsequent blood cultures were negative. After three days of treatment a retro-orbital abscess pointed beneath the lateral end of the supra-orbital ridge, and was incised. Culture showed nonhemolytic streptococcus. A small amount of dilute penicillin was instilled into the cavity. Within a few days the lesion had healed completely. There was no residual evidences of damage to orbital structures. (This case is reported through the courtesy of Captain Victor R. Alfaro, M.C., A.U.S.)

B. *Boils and Carbuncles:* We have treated few cases in this category because of the likelihood of spontaneous recovery and the shortage of the penicillin supply. However, there is every reason to believe that the manage-

ment of these cases will be improved through combining penicillin therapy with surgical removal of devitalized skin, fat and fascia. Checking of the spread of cellulitis and localization of the suppurative focus usually occurs within two or three days of commencing systemic therapy. After drainage is obtained the local irrigation of the wound with penicillin solutions containing 100 to 250 units per cc. seems to shorten the time of healing, but controlled observations of this effect are not yet forthcoming.

C. *Pulmonary Suppuration:* We have been especially interested in the possible usefulness of penicillin in the treatment of patients with pulmonary suppuration, and in the preoperative preparation of such cases as a means of reducing the incidence of postoperative pneumonia and empyema following lobectomy or pneumonectomy. The treatment of patients with chronic putrid lung abscesses has not yielded striking results, perhaps because many of the bacteria in these lesions are resistant to penicillin. The most that can be reasonably expected of the drug in these cases is to place the patients in better condition for operation and to reduce the incidence of postoperative infection of the pleural cavity.

Case 15.—G. C. (Fig. 20): *Diagnosis:* Chronic pulmonary suppuration.

A 70-year-old white male was admitted to the service of Dr. Charles Bailey, at Hahnemann Hospital, Philadelphia, October 26, 1943, for treatment of chronic pul-

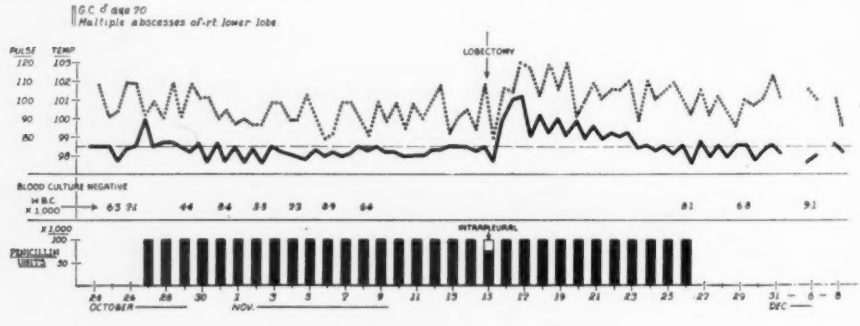

Fig. 20.

monary suppuration. His history was exceedingly complex, but the best clinical interpretation of his course was as follows: Perforation of a peptic ulcer in January, 1943, followed by a subphrenic abscess which ruptured first into the right pleural cavity, and then extended to involve the parenchyma of the right lower lobe. This drained spontaneously through the bronchus, but, in August, 1943, supplementary drainage was provided by thoracotomy. At the time of admission to Hahnemann Hospital he was chronically debilitated, and was raising two ounces of sputum a day, containing staphylococci, pneumococci and other mouth flora. His thoracotomy wound was still draining profusely. Penicillin was started on October 22, 1943, with 100,000 units per day intramuscularly, in preparation for lobectomy, which Doctor Bailey performed November 15, 1943. Right lower and middle lobes were removed and heavy contamination of the pleural space occurred from opening a mediastinal abscess and a collection of pus between diaphragm and lower lobe, and from division of the posterior sinus tract. The wound was closed except for a catheter drain, 25,000 units of penicillin was placed

in the cavity, and penicillin was continued by intravenous drip, and later intramuscularly, for two weeks. The patient was discharged December 8, 1943.

It is not our belief that prophylactic penicillin will eliminate the problem of empyema following contaminated lung resections. However, cases of this type offer encouragement to proceed with a careful estimation of the place of penicillin used in this way. A controlled study which is now in progress to evaluate this procedure has shown a much higher incidence of postoperative empyema in controls than in patients given penicillin before and after operation. This study will be reported at a later date.

When the lung abscess is due to infection with *Staphylococcus aureus* in pure culture it appears that penicillin will at times aid in bringing about a cure without the need for resort to surgery.

Case 16.—T. S. (Figs. 21, 22, 23, 24 and 25): *Diagnosis:* Acute lung abscess; *Staphylococcus aureus.*

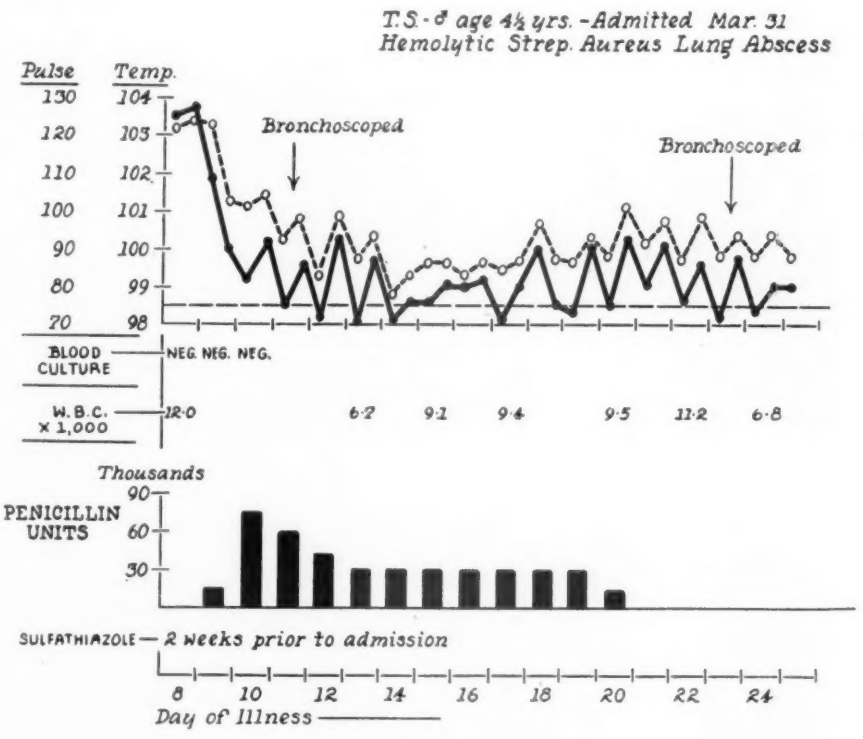

Fig. 21.

A four and one-half-year-old boy developed severe cough and pain in the chest following measles, and was admitted to the Children's Hospital March 23, 1943. Roentgenograms, March 27, showed a large abscess of the left upper lobe with fluid level. Bronchoscopic aspiration on March 29 yielded pure culture of *Staphylococcus aureus.* Despite sulfonamide therapy, the patient's condition deteriorated and the

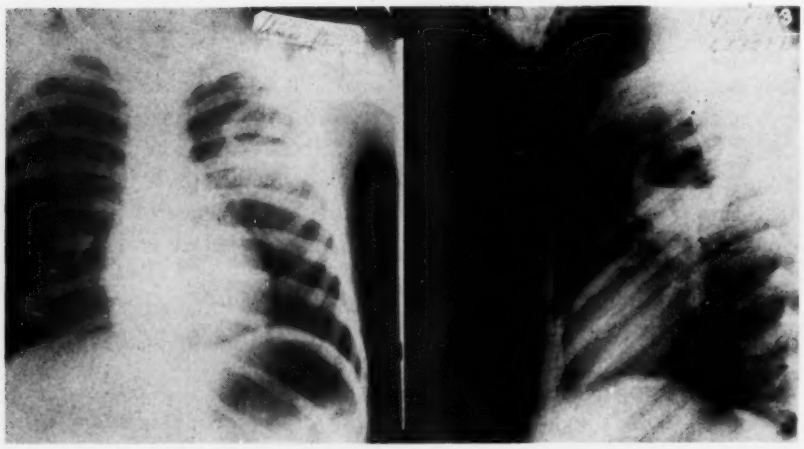

FIG. 22.—T. S. Hemolytic Strep. aureus—lung abscess x-ray of chest day before penicillin treatment was started.

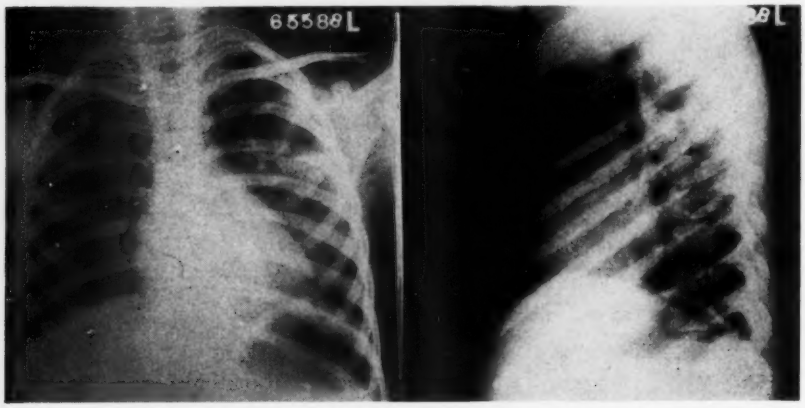

FIG. 23.—X-ray of chest four days after penicillin treatment was started.

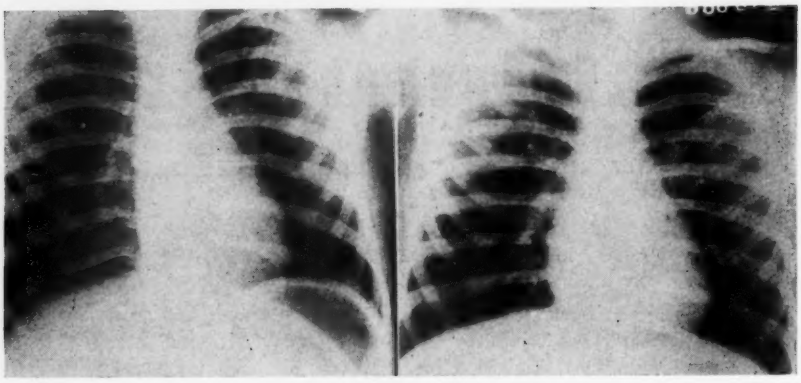

FIG. 24.—T. S. Hemolytic Strep. aureus—lung abscess x-ray of chest 7 days after penicillin treatment was started.

abscess enlarged. On April 2, 1943, penicillin treatment was commenced. A second bronchoscopic aspiration was performed the following day. Fever rapidly abated, and subsequent roentgenograms showed progressive disappearance of the abscess. He received a total of 415,000 units.

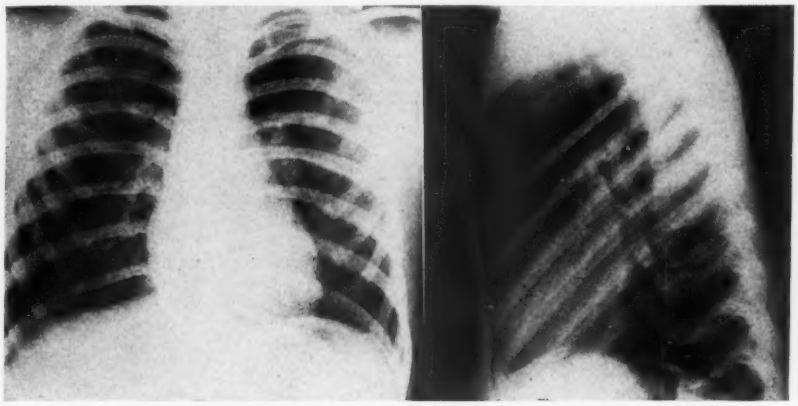

FIG. 25.—T. S. Hemolytic Strep. aureus—lung abscess x-ray of chest 5 days after penicillin treatment was started.

Penicillin cannot be expected to have a lasting curative effect in chronic bronchiectasis, but it may be used as a means of preparing septic cases for surgical treatment, though the striking effect brought out in the following case cannot be expected as a general rule.

Case 17.—B. F. (Fig. 26): *Diagnosis:* Chronic bronchiectasis.

This 16-year-old girl was admitted to the Hospital of the University of Pennsylvania under the care of Doctor Simon Leopold, July 29, 1943. She had rather extensive bronchiectasis, with symptoms extending back for ten years. The disease was largely

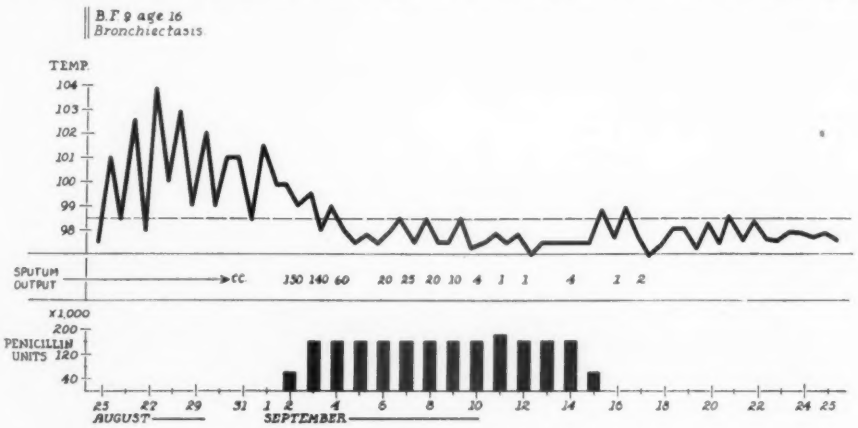

Fig. 26.

confined to the left lung, and the only contraindication to proceeding with lobectomy was the presence of active pulmonary infection. At the time of admission she had been running a spiking temperature for several months and was raising up to 200 cc. of sputum per day. Hemoglobin was 50 per cent; red blood count was 2,700,000; white

blood count was 18,000; and serum protein 6.2 Gm. per 100 cc. From August 2 to August 15 she received 120,000 units of penicillin daily. Her temperature immediately dropped to normal and her appetite and sense of well-being became greatly improved. The volume of sputum decreased abruptly and by August 15 was less than 1 cc. per day. Though no transfusions were given to her during this period, her hemoglobin rose to 79 per cent and the red blood count to 4,000,000. Unfortunately, she then developed a rather severe urticarial reaction to penicillin which necessitated termination of the treatment. Two weeks later Doctor Eliason was able to proceed with the first stage of a left lower lobectomy. During this interval there was no return of active lung infection. Her postoperative course, including the second stage, October 11, 1943, was uneventful, and attended by minimal febrile reaction to the surgical procedures.

This case is probably unusual in the degree of response to preoperative penicillin treatment. However, it illustrates how the drug may, in selected cases, not only control active parenchymal infection but also permit rapid

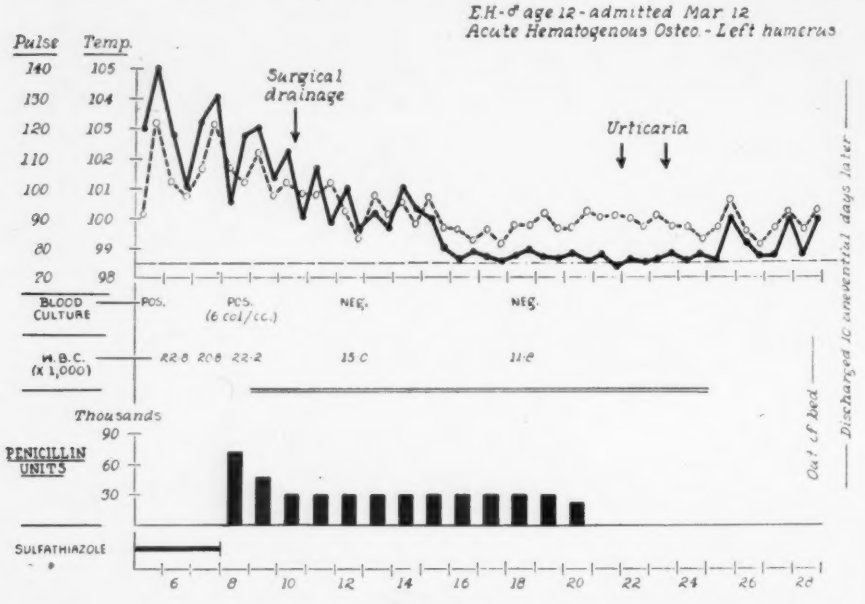

Fig. 27.

regeneration of blood and protein, and thereby improve the condition of the patient for a major operation.

LOCALIZED INFECTIONS IN BONE

A. *Acute Bone Lesions:* In cases of acute hematogenous osteomyelitis of long bones with or without bacteriemia, penicillin therapy will usually bring about rapid disappearance of evidences of disseminated sepsis, and there usually occurs a fairly prompt regression of the signs and symptoms of local inflammation at the site of localization. The development of roentgenologic evidence of bone destruction (if not apparent at initiation of treatment) will frequently be delayed. However, in spite of continuation of treatment for

FIG. 28 FIG. 29

FIG. 28.—E. H. Acute hematogenous osteomyelitis; Staph. aureus bacteriemia. X-ray of femur day penicillin was stopped.

FIG. 29.—E. H. Acute hematogenous osteomyelitis; Staph. aureus bacteriemia. X-ray of femur 10 days after last dose of penicillin.

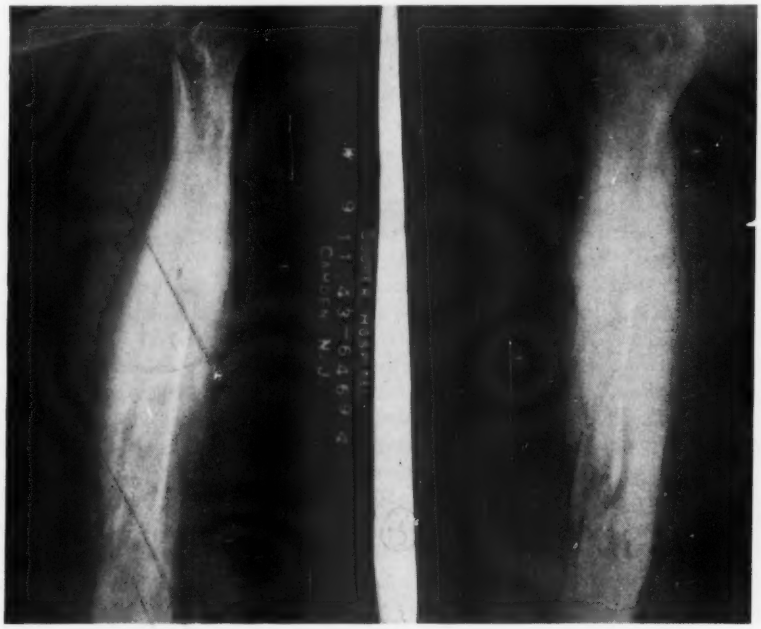

FIG. 30.—E. H. Acute hematogenous osteomyelitis; Staph. aureus bacteriemia. Follow-up x-ray of femur 5 months after treatment.

three to five weeks our cases have usually developed bone sequestra and have required surgical treatment to complete their recovery. Much more experience than is now available will be required to work out the new indications for surgical treatment of these cases. Penicillin treatment can undoubtedly be used to extend the applicability of the principle of withholding surgical intervention until a definite sequestrum has formed. Nothing has occurred in our experience to justify the hope that sequestra will become sterilized and reabsorbed, but simple areas of rarefaction in bone may occasionally become recalcified without drainage. Limitations in the supply of penicillin have prevented our treating these cases for several weeks after subsidence of the acute process, and this must be tried before final conclusions are reached.

Case 18.—E. H. (Figs. 27, 28, 29 and 30): *Diagnosis:* Acute hematogenous osteomyelitis; *Staphylococcus aureus* bacteriemia.

A 12-year-old white male, patient of Doctor B. F. Buzby, on March 17, 1943, entered Cooper Hospital, Camden, N. J., desperately ill with acute hematogenous osteomyelitis of the left humerus. Blood culture showed innnumerable colonies of hemolytic *Staphylococcus aureus.* After three days of ineffective treatment with sulfathiazole when all observers had despaired of the boy's recovery, penicillin was commenced at a dose of 80,000 units per day. Drainage of an abscess of the arm was performed two days later, but the bone was not touched. He improved progressively from the time the drug was started, blood culture became negative, and within a week his temperature became normal. The drainage wound failed to heal and six months later it was necessary for him to return for sequestrectomy.

This case brings out a fact which has been strongly impressed on us, that penicillin will quite regularly control the invasive features of acute osteomyelitis but will rarely, if ever, permit permanent avoidance of surgical intervention. Frequently this may be postponed, however, until a time of election. It remains to be determined whether the extent of the eventual sequestration could be minimized by early decompression of the medullary cavity of the bone.

Case 19.—T. McE. (Fig. 31): *Diagnosis:* Acute hematogenous osteomyelitis; *Staphylococcus aureus* bacteriemia.

This seven-year-old boy was first admitted to the Orthopedic Service of the Hospital of the University of Pennsylvania, August 5, 1943, with swelling and pain in the right lower thigh. Temperature was 106° F.; white blood count was 21,000; and the blood culture showed 147 colonies of *hemolytic Staphylococcus aureus* per cc. After 24 hours of sulfadiazine, when the blood culture was still positive, penicillin by continuous intravenous infusion was commenced in doses of 75,000 units per day. Signs developed of bronchopneumonia and fluid in the chest, and liver and spleen became quite enlarged. However, on the seventh day of treatment he was much improved. Roentgenograms were completely negative until August 16 when slight density of the periosteum at the midfemur appeared. This did not progress. By August 24 the leg tenderness had disappeared and the temperature remained normal thereafter. He was discharged, September 12, 1943, showing moderate palpable thickening of the left thigh. Pain in the left thigh recurred in October, 1943, and he was readmitted, at which time roentgenograms revealed areas of rarefaction and definite sequestrum formation. Low grade fever was present, and he was placed in a hip spica. Close follow-up during the ensuing

months revealed gradual increase in definition of the sequestrum and persistence of low-grade fever. Penicillin, at 100,000 units per day, was resumed on February 16, 1944. On February 21 the femur was explored, three sequestra were removed from a frankly purulent bed, and the bone was saucerized. Culture showed *hemolytic Staphylococcus aureus.* Temperature rose only to 100.2° F. following operation and was normal by the third day. Penicillin was discontinued on March 13 because of fever and urticaria. Since operation he has been treated by the Orr technic, and wound healing is progressively satisfactory.

B. *Chronic Osteomyelitis:* The procedure described by Lyons[7] for treatment of chronic bone suppuration in war wounds may be applied with considerable success to the treatment of chronic osteomyelitis of primarily hematogenous type. The administration of penicillin to patients with chronically draining sinuses harboring staphylococci or streptococci will usually bring about marked reduction in numbers or even disappearance of these

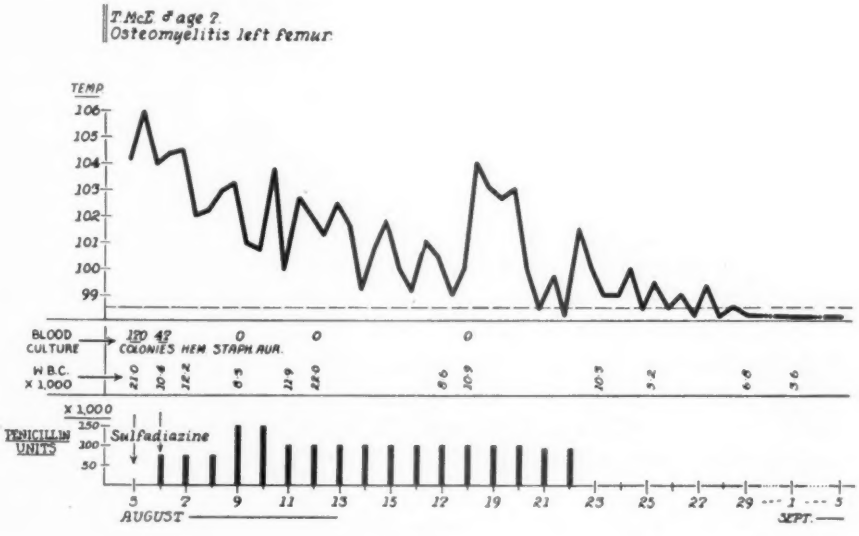

Fig. 31.

organisms in the exudate, but, direct culture of curettings from these sinuses may reveal persistent organisms not apparent on an ordinary swab culture. If no sequestrum is apparent roentgenologically the sinus may even become completely healed during the course of two or three weeks treatment. However, a fairly high incidence of late recurrences should be anticipated in cases where surgical removal of infected tissue is not carried out in conjunction with the course of penicillin.

In patients with surgically accessible lesions it is now our practice to administer penicillin for about a week, or until a definite bacteriologic response occurs. If repeated cultures show the exudate to be free of staphylococci we proceed with an operation which involves excision of the sinus tract and removal of all chronically infected granulation tissue and bone, guttering the

bone when necessary to gain access to involved areas. A small (No. 10) soft rubber catheter is laid in the wound and partial closure of the skin and subcutaneous tissue is effected around the catheter. A few cubic centimeters of penicillin-saline solution (250 units per cc.) are then instilled through the catheter every four hours for four to five days, while continuing the systemic administration of the drug in doses of 80,000 to 120,000 units per day for at least an additional ten days. The local penicillin may not be necessary but is employed as an extra precaution against allowing staphylococci to multiply on the freshly traumatized wound surface and in order to assure maximum freedom of contamination of the primary zone of inflammatory fixation. When the initial dressing is performed on the fourth or fifth day the wound appears to be perfectly clean, and healthy pink granulation tissue had begun to form. The catheter is then removed and packing loosely inserted in order to prevent premature closure of the skin over a dead space. As soon as the dead space has become filled with granulation tissue the packing is omitted and the wound surfaces are allowed to come together, and may even be encouraged to do so with flamed adhesive or sutures. By this procedure complete healing has been obtained in these cases in periods as brief as 15 days. The healing process resembles that which would be expected following excision of a simple exostosis. In some instances it might be possible to perform primary closure of the wound at the time of operation, but during the present exploratory period of penicillin study we have hesitated to take much liberty with the inevitable problem of the dead space occurring after removal of bone. It remains to be seen whether such a dead space can become filled in by organization of a sterile blood clot. It should be emphasized that we have employed the above procedure only in those cases in which the preliminary period of penicillin treatment has brought about complete, or virtually complete, disappearance of pathogenic organisms from the exudate, and where through débridement of the infected area has been possible. Orthodox treatment is required in those instances when organisms resistant to penicillin are present in substantial numbers after fourteen days of penicillin.

Case 20.—S. F.: *Diagnosis:* Chronic recurrent osteomyelitis.

This 22-year-old graduate student had had chronic osteomyelitis of many bones over a period of ten years. Operative procedures had always been followed by prolonged drainage and healing only after many weeks or months. At this admission he showed a medullary abscess in the lower femur at the site of a previous lesion. Sulfonamides failed to cause improvement, so penicillin was started on October 18, 1943. On October 22, we performed operative drainage and curettement of an abscess in bone, connecting with one in the soft part scar. Local penicillin treatment for five days was combined with continued systemic therapy. Marked reduction in number of staphylococci was evidenced by appearance of negative plates, though positive broth cultures continued. On the fifth day after operation the wound showed no clinical evidence of infection and was, therefore, encouraged to close by application of flamed adhesive. Plastic closure was later required because of muscle herniation, but primary healing took place. Six months follow-up shows no recurrence.

Case 21.—D. C. (Figs. 32, 33 and 34) : *Diagnosis:* Chronic osteomyelitis.

FIG. 32.—D. C. Chronic osteomyelitis. X-ray of femur 2½ months before penicillin treatment was started.

FIG. 33.—D. C. Chronic osteomyelitis. X-ray of femur 4 days after penicillin treatment was started.

FIG. 34.—D. C. Chronic osteomyelitis. X-ray of femur 2 weeks after penicillin treatment was stopped.

This was a complicated case of chronic osteomyelitis of the right femur of seven years duration in a colored woman, age 28. Culture from the draining sinus on the medial aspect of her right thigh showed *Staphylococcus aureus* and diphtheroids. She was given 50,000 units of penicillin daily from January 20, 1944, to February 3, 1944, when operative débridement of two bone abscesses was performed, together with excision of chronically infected scar tissue. The areas were not saucerized. No loose sequestra were found. Cultures at the time of operation showed no growth. Deep sutures were placed, but not tied, and the wound was packed with vaselined gauze. One week later the packing was removed, sutures were tied and a circular encasement applied. Penicillin was continued intramuscularly until February 24. The encasement was removed on this day, and by February 29 the wound was completely healed. Follow-up to-date shows no recurrence of infection.

Case 22.—M. H.: *Diagnosis:* Chronic osteomyelitis.

This 40-year-old female had had almost continuous suppurating wounds at the sacro-iliac region for seven years and in both ilio-inguinal regions for about one year. She had had many operations at all three sites, but always the infections had recurred and, with the infection becoming entrenched in bone it had become necessary to maintain drainage continuously. On admission to the Graduate Hospital of the University of Pennsylvania, June 7, 1943, the cultures from the sinuses showed *hemolytic Staphylococcus aureus.* Roentgenograms showed involvement of the fifth lumbar vertebra, sacrum, and both ilia. Penicillin was given by continuous intravenous drip, starting out at 100,000 units per day. Within ten days of starting treatment the patient began to feel better generally, the sacro-iliac wound was healed, and the exudate from the other sinuses became thin and serous. Cultures showed marked decrease in number of bacteria. On June 25 Doctor Harry Farrell performed a superficial excision of chronically infected scar tissue overlying the lesions in the ilio-inguinal regions and removed a small sequestrum from the left anterior superior spine. Nothing was done to the major bone lesions. Penicillin was discontinued on July 3, 1943, when the patient was allowed to go home. It was expected that she would need to return for further surgery, but within three weeks both wounds became completely healed. Subsequent follow-up has shown no recurrence of infection in any of the areas. It is surprising that recurrence of infection in the fifth lumbar vertebra has not taken place.

The prognosis of these cases regarding later recurrence must remain entirely guarded. Several years of continued follow-up will be required in order to determine whether the apparently clean healing of these wounds signifies a reduced likelihood of recurrent infection in comparison with those cases in which the formation of the scar takes place in the face of prolonged suppuration. We do believe that penicillin provides an entirely new and promising approach to the treatment of these troublesome problems. In bone cases it is especially important, however, to employ careful bacteriologic control at every step of the way.

Discussion: The foregoing review of experience with penicillin offers ample evidence of the fact that this drug does give promise of meeting the previously defined limitations of sulfonamide treatment of surgical infections. In this communication we have deliberately given emphasis to the favorable results that have been obtained with penicillin in selected types of cases, and we do not wish to convey the impression that results are likely to be uniformly as good as in many of the illustrative cases presented. Penicillin does appear to have a consistently favorable influence in cases in which the organism is susceptible, and in which the anatomic and pathologic characteristics of the

lesion are such as to permit the effective transport of the drug to the site of the infection; estimation of the possibilities and limitations of penicillin therapy in every individual case should be gauged in relation to this principle. In the more resistant lesions the effectiveness of the treatment can be enhanced by increasing dosage and by making full use of surgical procedures to eradicate resistant foci, in the expectation that the drug will prevent persistence of infection in tissues of normal architecture. The scope of antibiotic treatment will be extended if current research with new substances succeeds in producing a drug which will be effective against the gram-negative bacilli which now constitute the largest group of bacteria against which no highly specific agents have been developed. Fortunately, however, these gram-negative bacilli usually depend upon symbiosis with gram-positive organisms in maintaining a parasitic state in the body, and when the pyogenic species are eliminated with penicillin the resistant types prove to possess little pathogenicity.

SUMMARY AND CONCLUSIONS

1. Clinical studies on penicillin in surgical infections have been conducted during the past two years under the research program of the Committee on Chemotherapeutics and other Agents and the Subcommittee on Surgical Infections of the National Research Council. Authorization has been granted to issue a general statement of tentative conclusions which may be drawn from the authors' series of 440 cases.

2. Penicillin, when administered systemically, modified the course of most infections in which the causative organism is sensitive to penicillin *in vitro*. The magnitude of the effect in individual cases may be roughly classified as follows:

a. Dramatic curative responses in disseminated sepsis, particularly where circulation in localized distributing foci is adequate to effect contact between drug and bacteria. In such cases surgical treatment which would have seemed unavoidable in the past may, with penicillin, be postponed or avoided altogether.

b. Favorable responses characterized by subsidence of toxemia, correction of anemia, rapid healing of infected or seriously contaminated wounds, and elimination of infection within pleural cavity or joints.

c. Failures—particularly where the organism is insensitive, or where the lesion under treatment is attributable only in part (or not at all) to the persistent activity of penicillin-sensitive bacteria, and under conditions where penicillin cannot be brought to the infected area because of poor circulation or limited transport of the drug.

3. Local penicillin therapy needs further study, but is yielding encouraging results in special cases.

4. Just as with the sulfonamides, the use of penicillin requires a thorough redefinition of the indications for, and objectives in, the employment of surgery in treatment of localized infections.

5. Careful bacteriologic studies are essential if penicillin is to be used with maximal effectiveness.

6. As the supply of penicillin increases it will be possible through careful observation of cases, and the use of controls whenever practical, to reach a more accurate definition of the scope and limitations of penicillin than is yet possible.

REFERENCES

1 Morgan, H. (Brig. Gen., A. U. S.): In press.
2 Meleney, F. L.: J. Am. Med. Assoc., **124**, 1021, 1944.
3 Meleney, F. L.: **118**, 171, 1943.
4 Lockwood, J. S.: Surg., Gynec. and Obst. In press.
5 Fleming, A.: Brit. J. Exper. Path., **10**, 226, 1929.
6 Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: Lancet, **2**, 177, 1941.
7 Lyons, C. (Maj. A. U. S.): J. Am. Med. Assoc., **123**, 1007, 1943.
8 Keefer, C. S., Blake, F. G., Marshall, E. K., Jr., Lockwood, J. S., and Wood, W. B., Jr.: J. Am. Med. Assoc., **122**, 1217, 1943.
9 Dawson, M. H., and Hobby, G. L.: J. Am. Med. Assoc., **124**, 611, 1944.
10 Herrell, W. E.: J. Am. Med. Assoc., **124**, 622, 1944.
11 Bloomfield, A. L., Rantz, L. A., and Kirby, W. M. M.: J. Am. Med. Assoc., **124**, 627, 1944.
12 Abraham, E. P., and Chain, E.: Nature, **146**, 837, 1940.
13 Rammelkamp, C. H., and Keefer, C. S.: J. Clin. Invest., **22**, 425, 1943.
14 Florey, M. E., and Williams, E. O.: Lancet, **1**, 73, 1944.
15 Clark, A. M., Colebrook, L., Gibson, T., Thomas, M. L., and Foster, A.: Lancet, **1**, 605, 1943.
16 Garrod, L. P.: Brit. M. Jour., **2**, 755, 1943.
17 Rammelkamp, C. H.: Proc. Soc. Exper. Biol. and Med., **51**, 950, 1942.
18 Foster, J. W.: J. Biol. Chem., **144**, 285, 1942.

DISCUSSION.—DR. FRANK L. MELENEY, New York: Penicillin has been allotted to the units studying surgical infections under government OSRD contracts for two purposes; one, prophylactic—the prevention of infection in civilian contaminated wounds and burns, similar to the study of the sulfonamides which has been going on during the past two years; and the other, the active treatment of established surgical infections.

It will take some time to gather and analyze the data on prophylaxis with penicillin. It has only been available for the last six months for the study of compound fractures of the long bones of the lower extremity in four units, and the numbers are not yet sufficient to permit drawing conclusions.

Penicillin has been available somewhat longer in these Units for appraisal in established surgical infections, and more of these cases have been available. Doctor Lockwood's Unit has had the broadest experience of any of the Units, having treated 440 established infections with penicillin, and at least half of these cases have been surgical infections. This is the largest group of surgical infections in civilians that have been reviewed. We had, of course, Doctor Lyon's fine paper reporting the results of his treatment of returned soldiers, mostly with infected compound fractures, all of whom, I would like to point out to Doctor Key, had had sulfonamides.

Let me reiterate the fact that the appraisal of drugs is more difficult in surgical infections than in medical infections, because surgical infections are characterized by a local breakdown of tissue or a confined localized exudate which must be evacuated either spontaneously or by a surgical procedure, or must be absorbed by the body.

These necrotic exudative foci may prevent the entrance of the therapeutic agent or nullify its action when it gets to the focus. Furthermore, the rapidity of recovery from such infection depends greatly upon the time relationships between the onset of the infection, the administration of the drug, and the surgical procedure.

The problem of the appraisal of drugs in surgical infections is, therefore, much more complicated than in medical infections.

Drug therapy may be said to be effective in surgical infections, either (1) if it obviates the surgical procedure entirely; (2) if it permits a more limited type of surgical procedure than would otherwise be necessary; (3) if it permits primary closure immediately after removal of the dead tissue or exudate; (4) if it permits earlier secondary closure than usual; and (5) if it shortens the time of the control of the infection.

The first and third of these five criteria are fairly clear-cut, namely, obviating surgery and permitting immediate primary closure. The other three are comparative, and drug-treated cases must be compared with adequate controls.

Surgical infections also permit the local as well as the general administration of drugs, and this offers three methods to be appraised—local, general and both combined—with the necessity of considering the local and general toxic effects as well as the therapeutic effects of the drug.

As Doctor Lockwood has pointed out, both the sulfonamides and penicillin have brought out the importance of determining the exact bacterial etiology of the infection under consideration. Neither of them should be used indiscriminately. Penicillin has the very great advantage over the sulfonamides in that (1) its toxic limit (and I do not know whether that has ever been determined for man) is far above its therapeutic level; (2) it is not inhibited by blood or pus or necrotic tissue; and (3) when used locally it minimizes and does not increase exudate.

Penicillin has the disadvantage, however, of being inactivated or inhibited by many of the gram-negative bacilli, and of not working well when there are mixtures of organisms. In fact, its outstanding performance in surgical infections has been in those cases in which the causative organism has been the *hemolytic Staphylococcus aureus*, where the sulfonamides have fallen down so badly.

The unit at the Presbyterian Hospital has been able to study about 150 established surgical infections treated with penicillin, and about one-third of these were treated locally only.

In this respect our experience has differed considerably from Doctor Lockwood's, and in this field I think there is a possibility of wide usefulness of this drug with a minimum expenditure of material. Results have been obtained by local use alone, which I believe fulfill some of the criteria of effectiveness mentioned above.

I would like to show three slides to illustrate the value of local penicillin and two others to illustrate other points.

Chart 1 is a case of a very large abscess of the axilla due to an hemolytic streptococcus. On the second day it was aspirated without much change, although 400 cc. of pus was removed. On the 4th day a small incision was made at the bottom of the abscess, allowing the exudate to come out, and, through a tube, penicillin was introduced every three hours in 5,000 unit quantity. The immediate response was remarkable.

This is the combination of a minor surgical procedure with the local use of penicillin; 40,000 units were used each day, and it was stopped after six days. I believe, now, that we might have used very much less penicillin locally than we did, and could have given it less frequently.

Chart II is a case referred by Dr. William White, of our Association—that of a girl who had had two large abscesses of the face which had been operated upon, leaving scars. She had a third large abscess of the cheek which bulged into the mouth, and when he sent her to me he said: "If possible make your incision within the mouth rather than on the outside, to avoid another visible scar."

There was a tiny opening, however, on the outside through which, with a blunt needle, penicillin could be introduced. This was instilled daily, with from 2,500 to 3,500 units a day. There was prompt subsidence of the inflammation, and no incision was necessary at all.

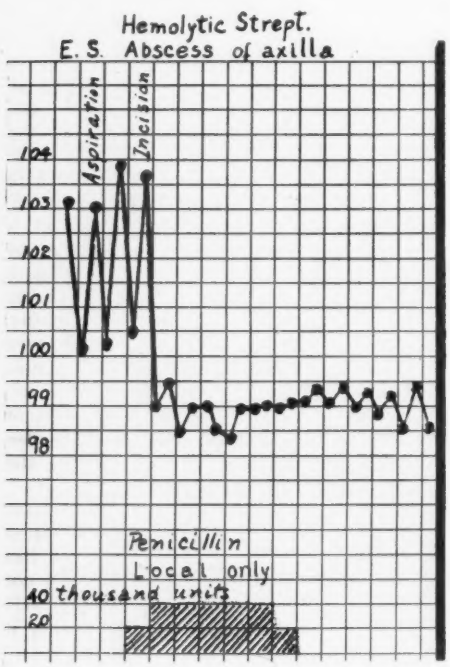

CHART I

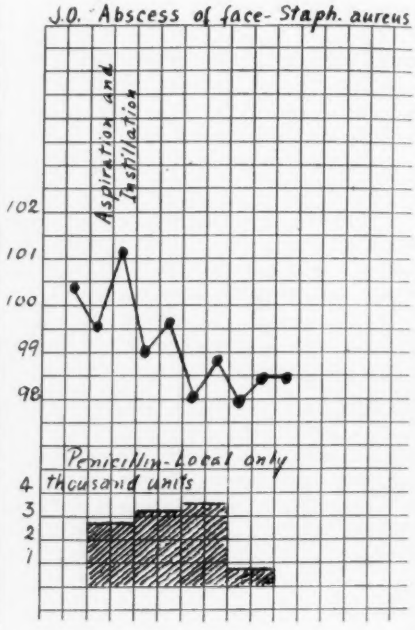

CHART II

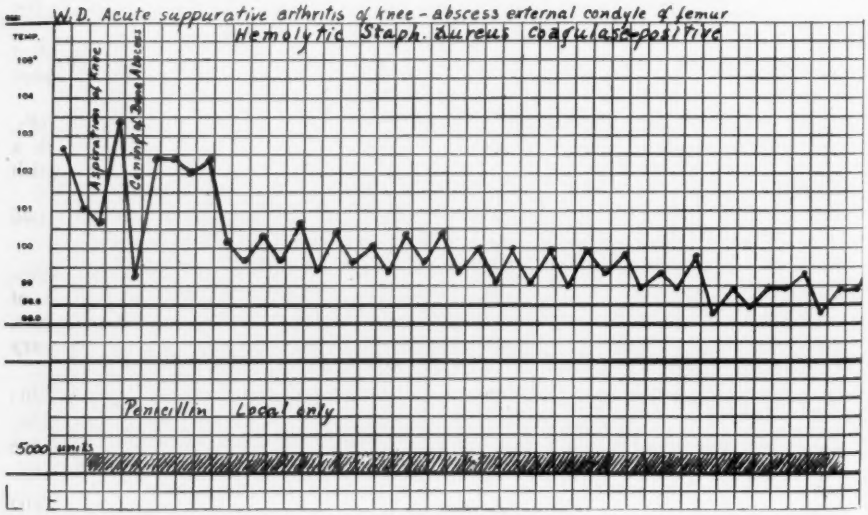

CHART III

Chart III is a case who had an acute abscess in the external condyle of the femur with an acute suppurative arthritis of the knee. When this patient was admitted, the knee was aspirated, and 5,000 units of penicillin were introduced. I planned the next day to open the knee joint as well as drain the abscess in the bone, but the knee showed no reaccumulation of fluid, so the bone cavity was unroofed and a China silk tampon was placed within the cavity, with 5,000 units of penicillin on gauze packing within the silk

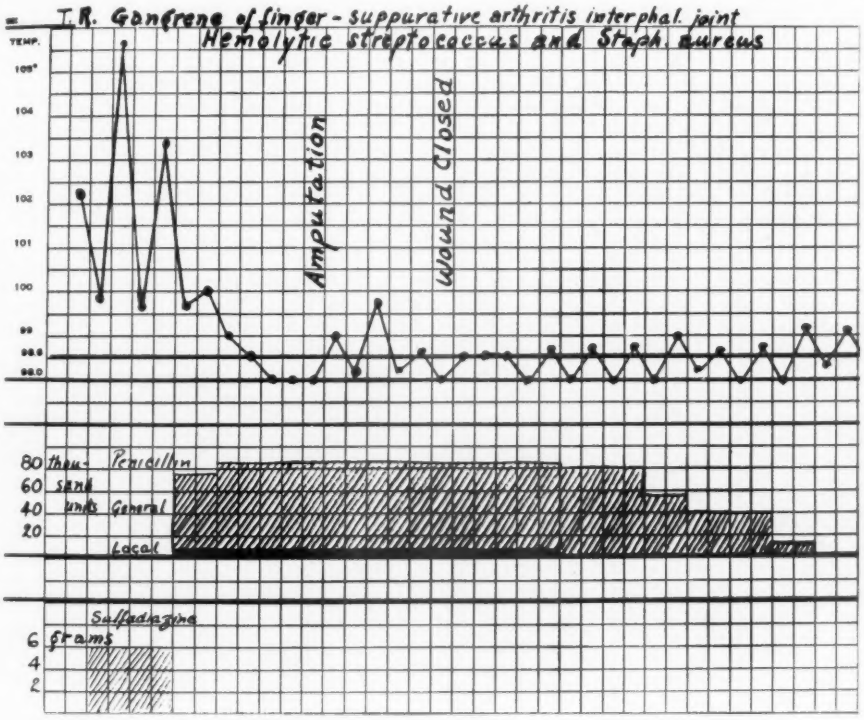

CHART IV

tampon. The packing was replaced daily, and the response was gratifying. When the silk tampon was removed on the ninth day, the bone cavity was lined with granulations. He was out of the hospital on the 26th day. The wound was all healed in less than six weeks, and he had perfect function of his knee joint, which received only one instillation of penicillin, and was not opened.

Chart IV illustrates a late primary closure. The patient was a young merchant-marine cadet, with an acute suppurative arthritis of the first interphalangeal joint of the left index finger. The infection, with both *hemolytic Staphylococcus aurus* and *hemolytic Streptococcus,* had dissolved the extension tendon and the joint surfaces. Amputation was performed through the joint, with a long anterior flap, which was left open. He received both local and general penicillin. The exudate ceased, the streptococci disappeared from the wound, and the staphylococci was greatly diminished in numbers. The wound was closed on the third day, and healed without any evidence of infection, penicillin being continued locally by instilling between the stitches once daily for three days and general penicillin being continued for five days more.

Chart V illustrates two cases of gas gangrene. The curve on the left shows a case of acute gaseous gangrene of the abdominal wall which followed drainage of the common

duct after removal of a common duct stone. The wound was opened up and the necrotic muscle removed and local zinc peroxide was applied—50,000 units of penicillin were given intravenously every three hours. Antigas gangrene serum in large doses was given. The temperature fell next morning, but she developed jaundice and suddenly died.

On the right of the chart is shown the temperature curve of the patient with a *Clostridium sordelii* infection. It is very rare of course. The jelly-like edema spread rapidly, in spite of wide incisions, and 50,000 units of penicillin every three hours. In this case there was no evidence of any effect, the temperature rising steadily until death.

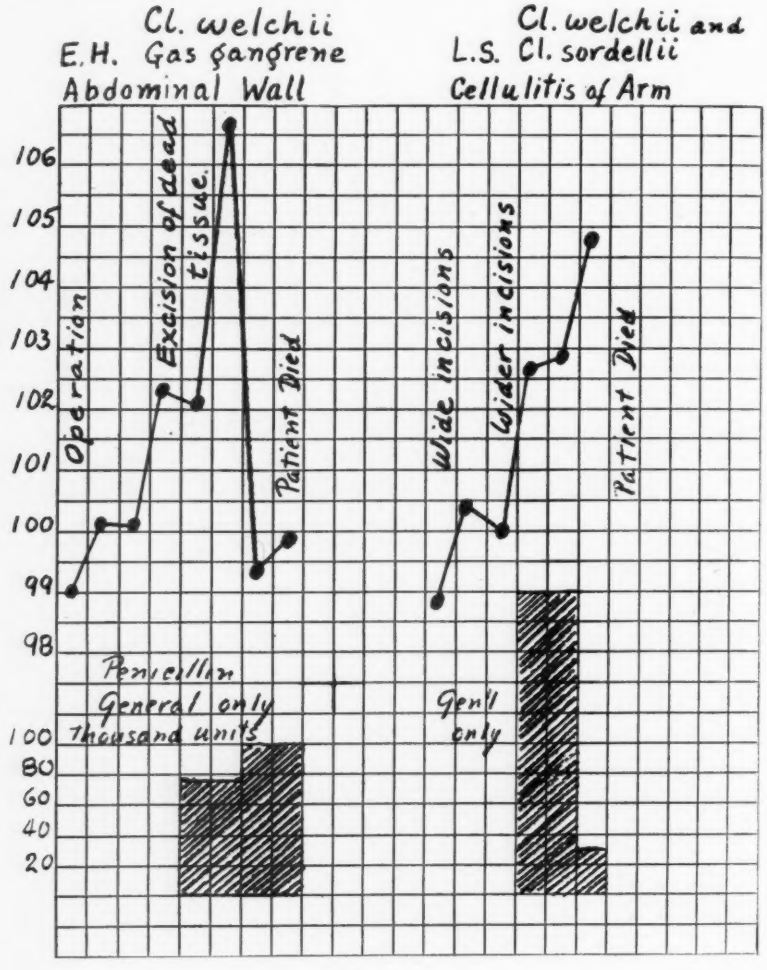

Chart V

In conclusion, I would like to simply say that the evidence seems to be slowly mounting that penicillin is going to meet the great need of preventing the general spread of infection from a local process due to the *hemolytic Staphylococcus aureus,* just as the sulfonamides have prevented the generalized spread of infections due to the *hemolytic Streptococcus.* Where the process is well localized, the local use of penicillin frequently hastens the control of infection, and may obviate a surgical procedure.

Penicillin has not satisfactorily met the problem of gas gangrene, and this may be due not only to the greater resistance of the causative organisms but to the fact that gas gangrene is a polymicrobic disease with gram-negative organisms frequently present, which frequently inhibit the action of penicillin. This is also true of other war wounds, and time alone will tell whether it is going to be effective in cutting down the incidence of local infection in damaged tissues.

One report, received very recently, indicates that it has not done so thus far. The immediate need is apparent for intensive work to be done to find something that will knockout these penicillin inhibitors—the gram-negative bacilli. Whether that will be in the field of chemotherapy or antibiotics, time alone will tell.

ACUTE STARVATION FOLLOWING OPERATION OR INJURY: WITH SPECIAL REFERENCE TO CALORIC AND PROTEIN NEEDS*

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IN HIS CLASSIC TEXT,[14] Lusk defines starvation as the "deprivation of an organism of any or all of the elements necessary to its nutrition." These nutritional elements, six in number, *i.e.*, water, salt, protein, fat, carbohydrate and vitamins, must each be considered in discussing starvation not only to achieve completeness, but because they are biochemically interdependent. For example, certain of the vitamins are now known to be necessary for the metabolism of carbohydrate. Carbohydrate, moreover, seems to be necessary for the proper utilization of protein. Of most significance is the fact that water and electrolyte balance is greatly disturbed by protein deficiencies due, in part at least, to a lowering in the concentration of plasma protein.

In actual surgical practice measures nearly always are taken to prevent water and electrolyte starvation; this is not particularly difficult, even when patients are unable to take anything by mouth, by the simple injection of physiologic saline solution. In addition, most patients receive a certain amount of carbohydrate sufficient at least to prevent ketosis, though usually insufficient to meet all of the caloric needs. Vitamins, neglected for a great many years, now are given adequately even if the patient is unable to take any by mouth. The remaining elements are fat and protein. For the present discussion, fat and carbohydrate will be considered under the one heading of caloric or energy requirements. This, strictly, is not justified over long periods, inasmuch as fat contains food essentials entirely apart from its calorogenic function. However, during short periods these considerations may be overlooked and caloric requirements, therefore, will be considered as one food essential regardless of whether it originates from fat or carbohydrate. Thus, acute starvation in most surgical patients probably is confined to protein and caloric (energy) needs, and most of the present discussion will be devoted to them.

Deprivation of protein and caloric needs wholly or partially, although frequent, is, in general, viewed with complacency or considered inevitable. The supposition that tissue and other stores will supply safely the needs of the body has lulled us into a false security; as a result many surgeons are not aware of the deleterious results produced by such starvation, even though manifestations may be subclinical. Wastage of body tissue, particularly tissue and plasma protein, is not without untoward effects which begin

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almost at once after protein is removed from the diet. Thus, it becomes important to study the causes and the effects as well as the means for the prevention and cure of starvation. Such study will undoubtedly lead to a more rapid and uncomplicated convalescence and raise surgical therapy to a higher plane of efficiency.

CAUSES OF STARVATION AFTER INJURY OR OPERATION

Only patients well-nourished at the time of injury or operation will be considered herein. For the sake of brevity, cases will be eliminated in which starvation is due to economic or other causes or to diseases themselves responsible for malnutrition.

When a healthy, well-nourished individual sustains a serious injury or undergoes a severe operation, starvation nearly always ensues. While the causes of such starvation are those which lead to deprivation of one or more of the nutritional elements, there is another factor which increases the need for one of them. As a result of injury, as shown so well by Cuthbertson,[6] there follows an unusually large breakdown of protein tissue, usually called "toxic destruction of protein," which leads to protein depletion even with the intake of a normal well-balanced diet. Although it is probable that an unusually large protein intake may prevent such loss of protein tissue, further study of the nature of this phenomenon is needed. Similar in its effect is the abnormal loss of protein in discharges or exudates of one type or another, as in peritonitis, empyema, burns, damaged tissue, or from large open wounds.

Even though the food requirements are normal and the patient is able to eat, the dietary intake after injury or operation is nearly always inadequate, due to several causes. Starvation is often imposed by the surgeon in charge because he fears that the ingestion of food will prove deleterious. Sometimes the patient himself is apprehensive. Often only fruit juices and broth are permitted; such an intake leads to electrolyte or protein starvation or both. Excluding cases in which it is necessary to keep the gastro-intestinal tract at rest as in general peritonitis, or in which vomiting is present, such fear is usually without foundation. On the other hand, when the patient cannot eat or is vomiting, protein starvation will ensue because the usual parenteral injections contain only electrolyte and glucose.

Starvation in other patients, while not imposed, is due to partial or complete loss of appetite, which is a frequent manifestation after injury or operation, aggravated often by oversedation, particularly the frequent use of morphine. Thus, there follows a failure in the normal impulses which ordinarily insure an adequate intake of food, and the patient, left to his own resources, does not eat, even when perfectly adequate trays of food are served. Ordinarily, anorexia ends quickly and spontaneously and the patient soon begins to eat of his own accord; however, in many cases, anorexia persists and becomes a manifestation of starvation itself. Thus a vicious cycle is established by which the very effect of starvation becomes a further cause.

THE EFFECTS OF ACUTE STARVATION AFTER INJURY OR OPERATION

The following manifestations are arranged in six arbitrary groups and are probably incomplete. As will be noted, most of the effects are due largely to protein starvation.

1. *Loss of weight* is of frequent, perhaps universal occurrence after severe injury or operation, even though its degree is perhaps not fully realized, and, indeed, may be partly masked in the most severe cases by retention of water. In a brief survey of our cases treated by the orthodox dietary regimen, loss of weight was universal and occasionally surprisingly great; for example, one patient suffered a decline of 25 pounds after a relatively uncomplicated cholecystectomy. Of particular interest in war surgery are the findings of Lyons,[16] who, in a series of compound fractures in American battle casualties, observed a loss of weight of from 5 to 30 kilograms (11 to 66 pounds).

Loss of body weight may not be a quantitative measure of the degree of starvation because changes in water content, which occupies 70 per cent of the body weight, are frequent and marked, and introduce a complicating factor. For example, nutritional edema may add many kilograms to body weight and even mask completely the wastage of body tissues. On the other hand, loss of weight in a patient with nutritional edema means absorption and excretion of the excess water, which is the first indication of *improvement* in the protein deficiency. Even in the absence of edema, increases in the extracellular fluid volume may add significantly to the body weight, as shown by Lyons,[16] and this also masks the actual degree of tissue loss. Moreover, water retention and excretion may also be influenced by a change from a high fat to a high carbohydrate diet or *vice versa,* respectively, as shown many years ago by Benedict and Carpenter.[1]

If water balance is maintained or its influence taken into account, loss of body weight means loss of body tissue, but its physiologic significance depends upon which of the two body tissue depots is depleted, *i.e.*, whether the loss affects the fatty or the protein tissue. Physiologic impairment follows depletion of tissue, including plasma protein, whereas adipose tissue can be used without such impairment; indeed, in the obese, loss of fat probably increases physiologic performance. The clinical significance of loss of body weight depends, therefore, upon the degree of protein depletion involved.

Loss of protein tissue can be measured clinically by the amount of nitrogen excreted, inasmuch as all protein tissue, when broken down, results in the terminal excretion of nitrogen largely as urea and ammonia. Actual studies have indeed shown that after injury or operation as much as 20 to 40 Gm. of nitrogen may be excreted per day. This (x 6.25) means 125 to 250 Gm. of protein or in terms of protein tissue, which is 80 per cent water, 0.6 to 1.3 kilograms (1.5 to 3 pounds). From this calculation it is easy to see how surgical patients are able to show such huge losses in body weight within a short period of time. By contrast, loss of fatty tissue to supply calories is much less. Even if all of, say, 2000 calories were supplied

by fat, this would represent but 200 Gm., or in terms of the tissue itself, which is but 20 per cent water, 240 gm. or one-half pound a day.

2. *Mild Clinical Manifestations.*—Surgeons are accustomed to attribute most of the postoperative weakness or asthenia to the operative procedure without realizing that much of it may actually be due to starvation, particularly deprivation of protein. According to Youmans[24] protein deficiency produces symptoms of fatigability and muscular weakness, which he states can scarcely be considered specific in the presence of deficiencies of other elements in the diet. However, in an interesting investigation by Mueller, Fickas and Cox,[17] normal humans ingested a diet complete in all elements except protein and found that after 48 hours severe symptoms of lassitude and asthenia developed which were corrected rapidly by the ingestion of protein food. Thorne, Quinby and Clinton[22] showed a similar influence of protein in an even shorter period of time by feeding a trained subject isocaloric breakfasts containing an abundance of fat, carbohydrate or protein. Only the meal with a high protein content failed to produce hypoglycemia and symptoms of hunger and lassitude after several hours. The present writer has often observed that postoperative weakness was improved by the intravenous injection of hydrolyzed protein.[9, 12] The most complete and convincing evidence, however, of the influence of food on postoperative asthenia is that described by Mulholland, Co Tui, *et al.*,[18] who showed how jejunal alimentation, beginning immediately after operation, alleviated most of these symptoms and accelerated convalescence in a series of gastric resections. Many factors are undoubtedly responsible for postoperative weakness and asthenia, but the evidence mentioned certainly suggests that starvation, particularly of protein, is of great significance.

3. *Serious Clinical Manifestations.*—Nutritional edema is probably one of the most important of the serious clinical manifestations of starvation and may involve the gastro-intestinal mucosa, producing severe symptoms, including those of intestinal obstruction.[19] Nutritional edema is probably also responsible for such phenomena as delay in wound healing, anuria and even circulatory impairment.[8] All of these complications have been observed after severe injury and operation, though often attributed to other causes. Although physical factors play a rôle, hypoproteinemia long has been recognized as the most significant cause of nutritional edema. A complete analysis of the important effects of starvation has been described at some length in the monograph of Jackson.[13]

4. *Lowered Resistance to Infection.*—The influence of starvation, particularly of protein, on the immunologic response of the body, has been studied by Cannon, Chase and Wissler.[4] They have shown that the production of antibody is but one-third to one-fifth as great in protein-deficient animals with hypoproteinemia as compared with those on a regular diet. It is probable from these important and convincing observations that many postoperative infections may be due in part to a lowering of the immunologic response of the body, which is secondary to protein starvation.

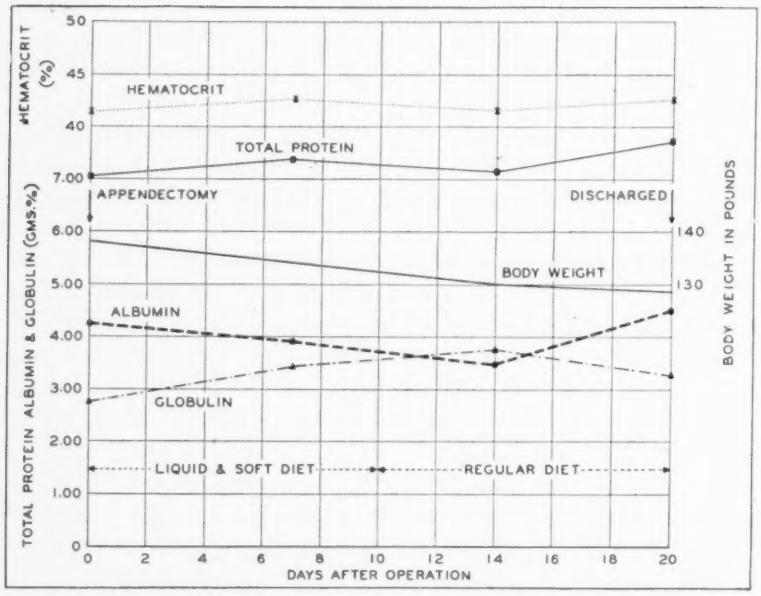

CHART 1.—Hypoproteinemia masked by hyperglobulinemia in a 55-year-old male following appendicectomy for acute appendicitis. Note the normal total protein; the fall in the level of plasma albumin was masked by a corresponding increase in the globulin fraction which was due to a moderate wound infection. There was a loss of eight pounds in body weight. Note the return of the albumin fraction to normal on resumption of a normal diet.

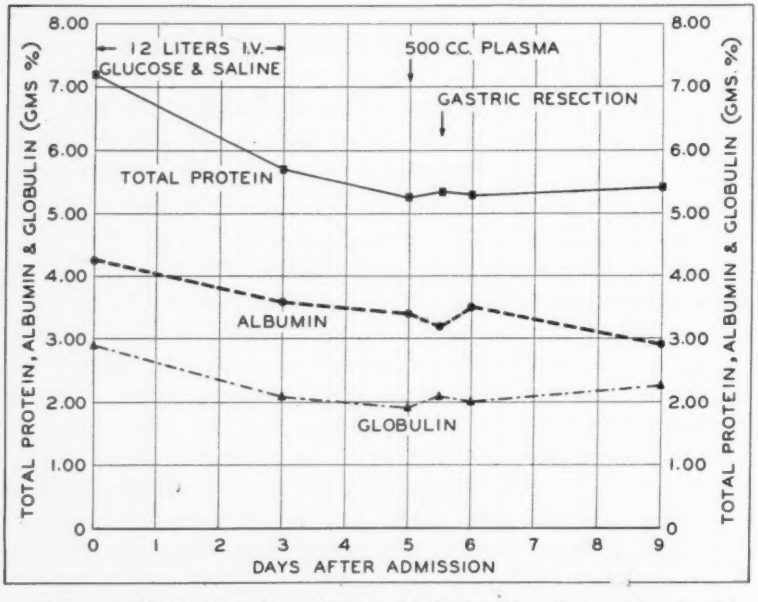

CHART 2.—Hypoproteinemia masked by dehydration in a 60-year-old male with pyloric obstruction due to carcinoma. Note the normal plasma protein on admission, although patient had lost 25 pounds in body weight; correction of dehydration by parenteral saline was accompanied by the appearance of hypoproteinemia which was uninfluenced by a 500 cc. plasma transfusion.

5. *Hypoproteinemia.*—A fall in the level of serum protein after operation or injury may be the first evidence of protein depletion, just as a fall in the vitamin C content of the blood precedes clinical signs of scurvy. Published data on the extent of hypoproteinemia after operation vary considerably, although Casten and Bodenheimer[5] have reported a postoperative fall in the total plasma protein concentration of 0.5 Gm. per cent or more in 20 to 100 per cent of their cases. Hypoproteinemia frequently escapes detection because its existence is masked by two factors discussed in a previous paper.[10] One of the factors is based upon the fact that the albumin fraction is the one significantly involved in malnutrition, yet many patients with hypo-albuminemia will show a normal value for total proteins because of an increase in the globulin fraction which often is due to infection. The other factor is dehydration, which is responsible for a normal concentration of both fractions, though the total amount of circulating protein is depleted. An example of each is presented herewith in Charts 1 and 2, respectively.

That a fall in circulating plasma protein occurs very promptly on withdrawal of protein from the diet has been demonstrated experimentally. Whatever stores of protein exist for the replacement of serum protein lost by hemorrhage, burns, *etc.*, they certainly do not seem to function when the protein is lost because of starvation. Thus, Weech[23] has shown very clearly, and his observations have been confirmed in our laboratory,[11] that the fall in plasma albumin begins with the very onset of a protein deficient diet. In the human, Cutting and Cutter[7] have confirmed these findings in a study of 26 normal individuals subjected to a 48-hour period of partial starvation. Even in this short period there was a fall of 10 per cent in the total amount of circulating plasma protein. Significantly, they showed that in spite of this loss the concentration of plasma protein was unchanged or even increased because of dehydration.

6. *Death.*—That a fatal outcome after injury or operation may be due to starvation certainly would be surprising in this land of plenty. Yet this has been an inescapable conclusion in several instances, although the recorded cause of death was, of course, the disease itself, or one of its complications. In such cases, extreme emaciation is the prominent finding at postmortem, with the surgical lesions corrected or of themselves insufficient to account for death. Inasmuch as death is an inevitable result of starvation in normal individuals, it is not surprising that those suffering from some injury or disease also may die because of an inadequate intake of food.

TREATMENT OF STARVATION

In most cases the treatment of starvation is astonishingly simple and consists merely of methods aimed at overcoming the patient's loss of appetite. To do so, however, the surgeon in charge must view anorexia as a therapeutic challenge, not as a necessary symptom. An adequate food intake is often possible even in the presence of severe anorexia if palatability is increased and nursing care provided. Idiosyncrasies may have to be given

consideration. Sedation, including morphine, should be used judiciously and bodily movement encouraged as much as possible. Moreover, the diet must be complete and in particular contain adequate protein. It is hard to understand the vogue of fruit juice, which contains merely carbohydrate and vitamin C, is entirely deficient in salt and protein,[2] and, thus, will lead inevitably to electrolyte and protein starvation when taken as the sole article of the diet. Ordinary broth, likewise, is an inadequate fluid, although a good source of salt, inasmuch as it contains in most cases a very tiny amount of protein; we have analyzed several broths and found less than one gram of protein in a cup of it. Milk is an excellent food and extremely valuable as a drink, although its water content is unnecessarily high. A much more concentrated and convenient high protein, high carbohydrate drink can be made up very readily by stirring 100 grams of skimmed milk powder into 200 cc. of water. This furnishes 34 grams of protein and 52 grams of carbohydrate, which exceeds that in a quart of milk, in one-fifth its volume. Three glasses of this liquid will meet the daily protein needs of a normal-sized adult. Solid food, as eggs and meat, should be added as soon as possible. Most postoperative patients can eat food much earlier than they are usually permitted to. In other words, eating should be encouraged rather than discouraged; often a simple statement by the surgeon will go a long way in overcoming anorexia and thus preventing starvation.

In spite of all that can be done with encouragement, special food and fluid, and nursing care, it is often difficult or impossible to get a patient, after operation or injury, to take a full, well balanced diet. Tube feeding may be employed, but has many obvious disadvantages. The actual amount of food necessary to furnish, say, 2000 calories, is fairly large and presents practical difficulties because of its bulk. This is especially true when feeding must be parenteral; for example, it would be necessary to inject each day eight liters of 5 per cent glucose to produce 1600 calories, the barely minimum requirement for an average-sized adult. The problem can be made easier by sacrificing some and perhaps even a considerable part of the caloric requirements. This is possible without producing serious physiologic impairment because caloric deprivation involves merely the loss of tissue fat, which may be considered as a nonessential tissue and thus is a true (dispensable) store of body food.

Caloric Versus Protein Requirement.—From the theoretic point of view, body fat should be able to supply a great deal of the energy requirements in the absence of caloric intake in food. Lusk[15] stated that under conditions of complete starvation about 87 per cent of the total energy actually is derived from tissue fat. This is an important consideration, inasmuch as 80 per cent of an ordinary well balanced diet consists of food furnishing calories, whereas but 20 per cent is protein. By dispensing with even part of the large proportion of the diet devoted to calories, the practical problem of postoperative nutrition becomes greatly simplified. How much of it can actually be sacrificed? A small amount of carbohydrate undoubtedly is necessary to prevent

ketosis. Moreover, Thomas[21] has shown that nitrogen balance cannot be achieved with protein alone. Brunschwig, Clarke and Corbin[3] could not achieve nitrogen balance with intravenous injections of hydrolyzed protein alone. What, actually, is the minimum amount of carbohydrate which is necessary in order to prevent ketosis and to insure adequate utilization of the ingested nitrogenous food? If this were known, starvation could be prevented with a relatively restricted diet without producing physiologic impairment. The minimum requirements then would consist merely of sufficient food to maintain water, electrolyte, nitrogen and vitamin balance. Caloric balance could thus be waived at the expense of tissue fat.

Evidence that nitrogen can be stored when the daily caloric requirement is reduced by 33 per cent was described by Rubner.[20] The present author for several years has injected a mixture of equal parts of glucose and hydrolyzed protein into patients intravenously and frequently observed positive nitrogen balance, even though the caloric intake was far from adequate to meet the daily needs. Further observations are in process to determine just how much of the caloric intake may be safely left to body fat. In the accompanying table the results of one preliminary experiment are described. Two dogs were given a diet consisting of different proportions of carbo-

TABLE I

NITROGEN (N.) BALANCE WITH TWO DIFFERENT PROPORTIONS OF PROTEIN AND CARBOHYDRATE
Note the larger and increasing retention of nitrogen with the high protein diet (2) as compared with the more normal proportion in diet 1

	Dog 1—Diet 1 20% Protein, 80% Carbohydrate			Dog 2—Diet 2 80% Protein, 20% Carbohydrate		
Periods	N. Intake	N. Output	N. Balance	N. Intake	N. Output	N. Balance
I (3 days)....	.32	.26	+.06	1.28	1.03	+.25
II (4 days)....	.32	.24	+.08	1.28	.93	+.35
III (4 days)....	.32	.29	+.03	1.28	.70	+.58
Average.....	.32	.26	+.06	1.28	.89	+.39

All figures are in grams per kilogram per day. The total caloric intake in each experiment was 40 per kilogram per day; this was probably inadequate because each dog was malnourished, having been on a deficient intake for the two weeks previously. The protein employed was dried scales of egg albumin (Merck), the carbohydrate Karo syrup. The nitrogen output included urine only; stools were scanty, and when analyzed amounted to but 5% of the urinary nitrogen.

hydrate and protein, the total being the same in each case, but insufficient to meet full caloric requirements. In one, the proportions were the same as in a normally balanced diet, 80 per cent carbohydrate, 20 per cent protein. Nitrogen balance was achieved in three successive periods, but was not very pronounced. In the other, the proportions were reversed so that the diet consisted of 80 per cent protein and 20 per cent carbohydrate; nitrogen balance was also achieved, but the degree increased with each succeeding period so that during the last period over ten times as much nitrogen was retained as compared with the last period in the first animal. The average nitrogen retained on the high protein, low carbohydrate diet was six times that of the nitrogen retained on the 80 per cent carbohydrate, 20 per cent protein diet, thus, indicating the superiority of an intake consisting largely

of protein, even though the amount of carbohydrate was low. Obviously, such a diet will tend to minimize greatly the tendency toward loss of protein tissue, and adds evidence to the justification for giving priority to protein over carbohydrate when a restricted diet becomes advisable or necessary. Other experiments, however, are in progress.

Prevention Versus Cure.—The effects of starvation, particularly when they are of long duration, are always difficult to overcome when they concern replacement of lost protein tissue. On the other hand, prevention of protein starvation is relatively simple. Thus, it should be emphasized as a principle of treatment that methods be established immediately after injury or operation to insure an adequate food intake so as to prevent the difficulties which arise when a severely malnourished patient must be treated. Prevention is not only important for this reason, but also because it will combat anorexia, which often persists because of starvation itself. Adequate nutrition from the very beginning, thus, breaks into the vicious circle mentioned above. This means that the surgical patient receives in his oral or parenteral diet at least 50, and preferably 100, grams of protein a day from the first day after operation or injury. This we have done and have observed definite alleviation of the above mentioned manifestations due to starvation. Moreover, appetite has returned much earlier, permitting a normal dietary regimen sooner than was previously the case.

COMMENT

Acute starvation after injury or operation, while prevalent, should not be viewed with complacency in view of the evidence herein assembled that definite physiologic impairment follows such starvation even of short duration. In most cases this deprivation is confined to caloric or protein needs. While most patients eventually get well in spite of starvation, it is probable that convalescence can be greatly shortened and complications minimized by avoiding such deficiencies. Food is so necessary for life in health that its importance in the injured would seem to be obvious, yet such a fundamental truth often escapes the surgeon in his care of patients after operation or injury.

Although the prevention of starvation can be achieved by insuring an adequate diet either by mouth or parenterally, evidence is presented to indicate that a large part of the caloric needs may safely be sacrificed for short periods without physiologic impairment provided an adequate protein intake is assured. While further observations are required to establish the soundness of this view, its practical importance is sufficient to warrant further studies. Since the caloric component of the diet is by far the largest, the possibility of waiving even a considerable part of it becomes an important consideration, particularly during periods when intravenous feeding is necessary. Such a priority of protein over caloric needs may also be important in war time, when healthy soldiers are deprived of their sources of supply and must subsist for many days on rations containing as little bulk as possible.

Under such conditions it may be more important to insure nitrogen balance with a high protein diet than to provide fat and carbohydrate for all of the caloric needs. Should loss of body weight occur as a result of starvation, clearly it is much more important that nonessential tissue fat rather than essential tissue and plasma protein be depleted.

SUMMARY

1. Acute starvation after injury or operation is usually confined to caloric and protein needs; though due to deprivation of these nutritional elements, excessive destruction and loss of protein is an important added factor.

2. Deprivation of protein is serious because it leads to early loss of tissue and plasma protein; deprivation of calories is less serious because it leads primarily to loss of nonessential fatty tissue.

3. The effects of starvation after operation or injury are due largely to protein deprivation and include a variety of mild and serious clinical manifestations. Hypoproteinemia is frequent after operation or injury but is often masked by dehydration or hyperglobulinemia.

4. Starvation may be avoided to a considerable extent by recognizing anorexia as a therapeutic challenge rather than an inevitable symptom.

5. Evidence is presented indicating much of the caloric need may safely be sacrificed provided adequate protein is furnished. In patients unable to take a full diet by mouth or receiving parenteral alimentation, such a restriction may prove of much practical value.

6. Because prevention of starvation is much easier than its cure, adequate nutrition should begin immediately after injury or operation.

BIBLIOGRAPHY

1 Benedict, F. G., and Carpenter, T. M.: Carnegie Inst. of Wash., 1910, page 110.
2 Bridges, M. A.: Food and Beverage Analysis. Lee & Febiger, 1935.
3 Brunschwig, A., Clarke, D. E., and Corbin, N.: ANNALS OF SURGERY, **115**, 1091, 1942.
4 Cannon, P. R., Chase, W. E., and Wissler, R. W.: J. Immunol., **47**, 133, 1943.
5 Casten, D., Bodenheimer, M., and Barcham, I., ANNALS OF SURGERY, **117**, 52, 1943.
6 Cuthbertson, D. P.: Lancet, April 11, 1942, p. 433.
7 Cutting, W. C., and Cutter, R. D.: Proc. Soc., **32**, 1053, 1935.
8 Elman, R.: J.A.M.A., **120**, 1, 1942.
9 Elman, R.: ANNALS OF SURGERY, **112**, 594, 1940.
10 Elman, R., and Lischer, C.: S. G. & O., **76**, 503, 1943.
11 Elman, R., Sachar, L. A., Horwitz, A., and Wolf, H.: Arch. Surg., **34**, 1064, 1942.
12 Elman, R., Weiner, D. O., and Bradley, E.: ANNALS OF SURGERY, **115**, 1160, 1942.
13 Jackson, C. M., Inanition and Malnutrition. Blakiston, 1925.
14 Lusk, G.: The Science of Nutrition. Saunders, 4th Edition, 1928, p. 75.
15 *Idem, ibid:* p. 91.
16 Lyons, C.: J.A.M.A., **123**, 1007, 1943.
17 Mueller, A. J., Fickas, D., and Cox, W. M., Jr.: Bull. Johns Hopkins Hosp., **72**, 110, 1943.
18 Mulholland, J. H., Co Tui, F., Wright, A. M., and Vinci, V. J.: ANNALS OF SURGERY, **117**, 512, 1943.
19 Ravdin, I. S., Stengel, A., and Prushankin, M.: J.A.M.A., **114**, 107, 1940.

[20] Rubner, N.: Quoted by Lusk, *ibid*, p. 365.
[21] Thomas, K.: Quoted by Lusk, *ibid*, p. 188.
[22] Thorn, C. W., Quinby, J. T., and Clinton, M.: Ann. Int. Med., **18**, 913, 1943.
[23] Weech, A. A.: Harvey Lectures, **34**, 57, 1938–39.
[24] Youmans, J. B.: Nutritional Deficiencies. Lippincott, 1941, p. 231.

DISCUSSION.—DR. CHARLES C. LUND, Boston: Doctor Elman has given us a good summary of the importance of protein in surgical patients. We are hearing more and more about this from various sources. Dr. Arthur Wright's group, and, of course, before that Doctor Ravdin, and many others, have studied it.

It came to my attention most strongly through our work on burns. I just want to call attention to two quantitative facts that may not be too generally appreciated as yet.

One is that, in general, with the slow development of a slight, long-time protein deficit, the plasma protein usually remains pretty nearly normal until there is a great decrease in the body stores, so at times one will find a patient with only a slight lowering in the plasma protein value, who will in fact be greatly depleted.

The other point I want to make is that you have to give protein nourishment either by mouth or, if intravenously, by protein digest, because it is impractical to give enough protein in the form of plasma or albumin to make up these deficits. You may have noticed in one of Doctor Elman's charts that 500 cc. of plasma were given, and had no effect at all on the plasma protein value.

The unit of plasma contains about 18 Gm. of protein, and the patient, to stay in balance without any great burden of illness, has got to have 75 Gm. of protein a day. If there is a particular loss or burden, he may need 200 or 300 Gm. a day to make it up, and that may have to be done over a long, long time. It just is not possible to get enough human plasma or human albumin to do anything more than tide over the greatest emergency for a very short time.

I want to emphasize, also, Doctor Elman's statement about the rapidity with which protein stores can be depleted under certain conditions, and the great difficulty of getting them back after they are depleted. Some of you will remember that last year I presented a case of burns that lost 50 pounds of weight in a period of about eight weeks. The vicious cycle was broken, but after 14 months he had gained back only two-thirds of that loss in weight, and I think we were fortunate that he recovered that much, compared to the known difficulties that exist in repairing such terrific depletions.

DR. EVARTS A. GRAHAM, St. Louis, Mo.: I think Doctor Elman has made a very important contribution in calling attention to this important fact about starvation which may occur right under our eyes.

I have been acquainted, of course, with Doctor Elman's work, which led up to this, and also the present work which he has reported here today. When he discussed this matter with me a good while ago, I mentioned the fact to him that this is one of those strange phenomena which take place, namely, that it was well known, and has been well known for a long time, that starvation does take place in surgical patients, but that it was something like the weather, and nobody seemed to do very much about it, and I thought it would be an admirable thing for him to do something about.

In the work of the Empyema Commission in World War I, Doctor Bell made a particular study of the nitrogen loss in patients with empyema, and his study is included in the report of the Empyema Commission. He called attention, at that time, to the great difficulty there was in keeping patients with empyema in nitrogen balance, and emphasized very strongly the importance of feeding these patients generously in order to keep up nitrogen equilibrium and to prevent them from losing weight, and thereby delaying their convalescence.

At that time, which was in 1918, 26 years ago, there were no satisfactory methods for studying plasma protein. The work had to be done almost entirely by studies of

nitrogen excretion in the urine. But that observation was very definite. It was clearly established; it was much commented on at the time; it was made much use of, and, as a matter of fact, I have tried ever since that time to emphasize to our own house staff the great importance and necessity of overfeeding patients with empyema in order to keep them from losing weight, with particular reference to the protein.

Unfortunately, unless one gives personal supervision to it, it is one of those things that is not done as it should be done, because its importance is not recognized. It is necessary, therefore, for somebody like Doctor Elman to come along, using more modern methods, to reemphasize the importance of watching the patient's food requirements, particularly his protein requirements.

We realize now, more than we did 26 years ago, that protein requirements are especially important, and, therefore, I am very glad to have Doctor Elman, shall I say, bring up this subject again with new methods, in order to emphasize the whole problem and the importance of it once more.

DR. PAUL R. CANNON, Chicago: Doctor Elman, in my opinion, is approaching the problem in the right way in stressing the basic significance of "starvation" in surgical prognosis. Surgeons, indeed, have an opportunity to study the surgical effects of starvation and to learn important facts about protein metabolism that may be applied to the treatment of starvation in general, for, after all, considering the fact that millions in India, China, and the occupied countries, are suffering from varying degrees of food scarcity it is probable that starvation is now one of the world's most important diseases.

In the field of medicine we must take our material where we find it; therefore, when surgeons are confronted with the facts of starvation it is their duty to study the disease itself.

Doctor Elman called attention to the difficulties of evaluating the significance of plasma protein concentrations because of the fact that with a declining albumin concentration and a rising globulin concentration the total protein concentration may remain in the normal range. We must recognize the fact, of course, that a blood protein determination reveals only the concentration of protein in the blood at one particular instant, and that it does not necessarily afford evidence of the state of the protein reserves. In thinking about the relationship between the plasma proteins and reserve proteins, a rough comparison may be made between the relationship of the level of water in a well shaft and the ground water reserve. When the well driller sinks a shaft into two types of soil, one with rich water reserves and the other with low reserves, he determines the state of these reserves by emptying the shaft and seeing how rapidly water comes back to a certain level. Similarly, in patients presumably who have lost considerable amounts of blood protein from protein reserves already depleted, the reestablishment of plasma protein concentrations will be slow. Therefore, when there is a history of malnutrition and loss of weight before operation one may assume depletion of the protein reserves regardless of the fact that because of the decrease of blood volume a total protein concentration from one determination may not actually reveal the state of the protein reserves.

SYMPOSIUM ON BURNS

THE HEALING OF DEEP THERMAL BURNS*

A PRELIMINARY REPORT

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IN THE TREATMENT of the local area in deep thermal burns the ultimate objective should be the grafting of skin at the earliest moment compatible with success and with a minimum mortality rate. The chief cause of delay in the healing of these wounds is, in effect, the continued presence of the slough. Such dead tissue is essentially powerless to combat infection; with it successful skin grafting is impossible and contracture continues. It is regarded as of signal importance, therefore, to effect the removal of the slough at the earliest moment. The advantage of this removal is fully realized, however, only when the resultant base of the wound is acceptable for immediate grafting with skin, and when there is no significant damage to living tissue.

Enzymatic digestion of the slough in wounds has recently received attention. Glasser (1940) reported success in this connection using a proteolytic compound containing papain. He cited the favorable results obtained in chronic otitis media by Tremble, using urea and caroid in a saturated aqueous solution. More recently, Cooper, Hodge and Beard (1943) reported on the use of an enzymatic digest for the removal of dead tissue. Howes (1943) noted that various enzymatic compounds were effective in removing the slough in wounds in from 24 to 48 hours. Several of these damaged living tissue. Howes also noted that the dead tissue was removed with more difficulty if the enzymatic compounds were first applied after several days.

It is well known that infection often hastens to a certain degree, but at a high price, the separation of the original slough in deep thermal burns. There is the general impression that the hydrogen ion concentration of the wound fluid is increased in many infected wounds, and this has been confirmed in our experiments. The results of preliminary experiments with the local application of various organic and inorganic acids revealed that the separation of the slough could be greatly hastened if the p_H of the surface of the wound was sufficiently lowered. A large series of acids have been studied in this connection, and it is now apparent that under proper conditions not only does the slough separate more rapidly than in the control wound, but

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Yale University.

Read before the American Surgical Association, May 3–4, 1944, Chicago, Ill.

the living tissue is not significantly damaged and the resultant base of the wound is such as to permit successful and immediate grafting with skin.

Pyruvic acid presents outstanding advantages within the objectives of this method of treatment. With it the necessary balance between p_H and concentration of the acid can be obtained in order to accomplish the desired results.

It is the purpose of this report to describe some of the pertinent experimental data concerning the use of this method in the treatment of deep thermal burns.

METHOD

Dogs were used, and anesthesia was obtained with intravenously administered nembutal. The hair over the trunk was clipped closely or shaved. Aseptic precautions were not used, and there was no further preparation of the skin.

Deep burns were produced by the direct application of a low blue gas flame to the skin for 20 seconds over the dorsolateral aspect of the trunk. This standard burn was from three to four centimeters in diameter, and uniformly involved the full-thickness of the skin.

In the *control* series the wounds were studied either concurrently with experimental wounds in the same animal, or in separate animals. In the first instance, the control and the experimental wounds were made on similar areas on opposite sides of the trunk, so that each animal served as its own control. In the latter instance, the control wounds were placed on separate animals, to preclude any possibility of their contamination with the solutions used on the experimental wounds.

The control wounds were dressed within a few hours after burning with either dry gauze, vaselined gauze or a paste consisting of 8 per cent cornstarch in distilled water. The dressings were changed every one to four days, and similar dressings reapplied.

The *experimental* wounds were dressed within a few hours after burning with a thick layer of paste consisting of a solution of pyruvic acid at a p_H of 1.9 and of 8 per cent cornstarch.* This was prepared by mixing a hot solution of pyruvic acid in distilled water at a p_H of 1.9 with the necessary amount of cornstarch suspended in a similar but cool solution. This paste was applied thickly on the surface of the wound and the adjacent skin and was held in place with gauze. This inner dressing was then covered with a layer of vaselined gauze. The dressings were changed daily or every two days.

In both the control wounds and the experimental wounds the dressings were securely held in place with an adhesive elastic bandage enclosing the trunk.

* It should be emphasized that the starch paste used in these studies was selected in order to avoid a complicated base during this phase of the work. From the standpoint of preliminary experimentation this is satisfactory, but it is not a desirable vehicle from the practical viewpoint. An oil-in-water emulsion is a satisfactory base in this connection.

All animals in which the dressings loosened, with exposure of the wounds, were deleted from this study, whether or not there was any evidence of additional trauma to the wounds. The dressings were carried out usually under light anesthesia with intravenous nembutal so as to eliminate the possibility of trauma to the wounds from the struggling of the animal during the dressing.

The skin grafts were taken from the thigh or trunk of the same animals, and were cut with the Padgett-Hood dermatome set at $^{16}/_{1000}$ of an inch. The grafts were sutured in place with fine silk or were merely "snubbed" on with pressure. The grafted wound was covered with a layer of *tulle gras*, and a bulky pressure dressing applied.

RESULTS

Control Group.—(20 wounds): Whether the control wound is on a symmetrical area on the side of the trunk opposite an experimental wound or on a separate animal, the complete separation of the slough requires from 10 to 12 days. The slough softens on its surface and breaks up into many pieces which are firmly adherent. During the week before complete separation the wound is covered with a necrotic, stringy adherent layer (Figs. 1 and 2).

Healing takes place by contracture and by the marginal ingrowth of epithelium, without the appearance of islands of epithelium within the wound. Such a standard burn may, therefore, be classified as a deep one.

Experimental Group.—(20 wounds): In the experimental series the slough separates completely within 72 hours (Figs. 3 and 4).

The manner of separation of the slough under these circumstances is of particular significance. Separation appears to begin at the periphery where, in 24 to 36 hours, there is slight softening. A plane of cleavage develops beneath the otherwise intact slough, and separation proceeds centralwards. After 48 hours the cleavage has developed to the point where the slough, aside from soft dermal tags at the periphery, is either completely free

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FIG. 1.—Control Wound: Standard deep thermal burn on the dorsolateral aspect of the trunk of the dog, five days after burning. Original burn similar to that shown in Figure 3, and produced by the same method. Treated with pressure dressing of dry gauze. Note adherent slough.

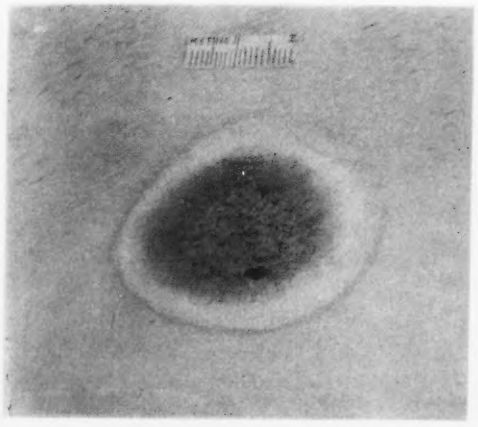
FIG. 2.—Control Wound: Same wound as shown in Figure 1, ten days after burning. Slough separating piecemeal, but still adherent in many areas. Dressings had been changed on the second, fifth, eighth and tenth days after burning.

FIG. 3.—Experimental Wound: Standard deep thermal burn on the dorsolateral aspect of the trunk of the dog, 30 minutes after burning. 3.8 × 3.1 cm. Burn produced by direct application of a low blue gas flame for 20 seconds.

FIG. 4.—Experimental Wound: Same wound as in Figure 3, 72 hours after burning. Treated with a daily application of a thick layer of pyruvic acid paste at a *p*H of 1.9, beginning one hour after burning.
Slough separated completely. Note the clean, healthy base of the wound.
Central part of the wound grafted on this day with a split-graft cut at 16/1000 of an inch, to include an adequate dermal pad. Wound covered with a tulle gras and pressure dressing.

FIG. 5.—Experimental Wound: Same wound as in Figures 3 and 4, five days after burning; two days after grafting of central area. Living graft and healthy granulation tissue.

FIG. 6.—Experimental Wound: Same wound as in Figures 3–5, 16 days after burning; 13 days after grafting. Note the living graft and epithelial proliferation at the margin of the graft and of the wound. Still no evidence of skin islands in the ungrafted area.



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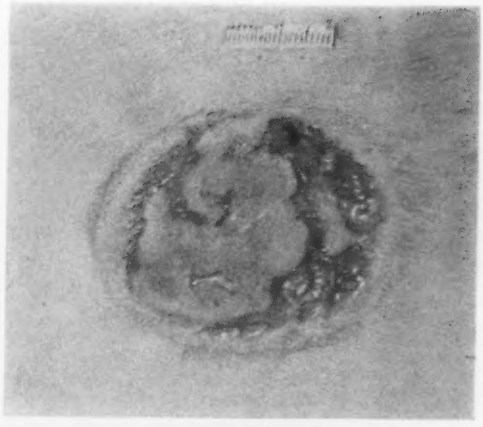

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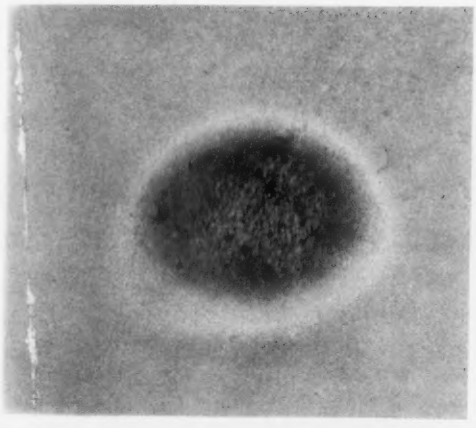

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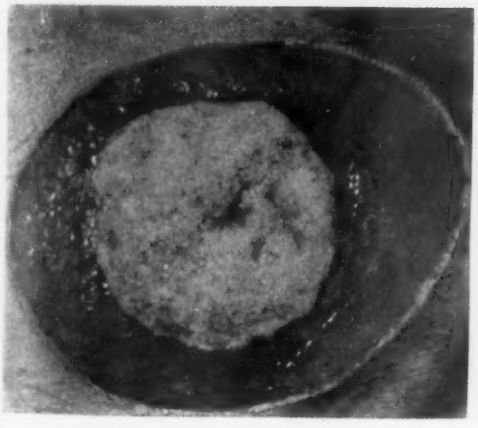

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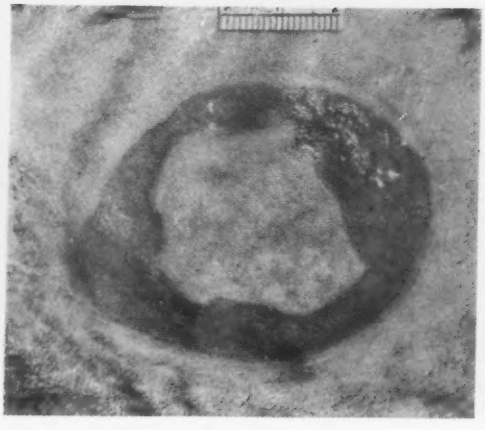

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FIG. 7.—Experimental Wound: Deep thermal burn in the dog, similar to that shown in Figure 3, 66 hours after burning. Treated daily with a thick layer of pyruvic acid paste at a *p*H of 1.9. Shown to illustrate the manner of separation of the slough, which is completely free beneath and is attached only by soft peripheral dermal tags. The intact central slough is rubbery, without evidence of digestion on the surface.

FIG. 8.—W. P., N. H. H., Unit B4705: Deep fire burn in a four-year-old boy at time of admission to the hospital, one week after burning. Wound had been treated at home with various ointments and signs of local infection had developed. Culture of necrotic tissue revealed hem. Strep., hem. Staph. aureus, gram-negative bacilli and enterococci.

Treated with a generous application of pyruvic acid paste at a *p*H of 1.9, with the dressing sealed with vaselined gauze. First dressing on the third day after admission, at which time 40 per cent of the slough had separated. Similar dressing reapplied on the third and fifth days after admission.

FIG. 9.—Same burn as shown in Figure 8, six days after admission. Slough completely separated, clean granulating base, with unusual vascularity. No evidence of damage to adjacent unburned skin.

The wound was obviously ready for grafting but was treated for an additional four days with the same paste, without evidence of injury to the exposed base. Split-grafts applied after this additional treatment, on the tenth day after admission.

FIG. 10.—Same wound as shown in Figures 8 and 9, ten days after grafting. The margins of the wound were not trimmed at the time of grafting.

FIG. 11.—Same wound as shown in Figures 8–10, five weeks after admission, with protective dressings no longer necessary. Patient ambulant.

FIG. 12.—Opposite side of the same leg, with a burn similar to that shown in Figures 8–11, treated in a similar manner.

Final result five weeks after admission.

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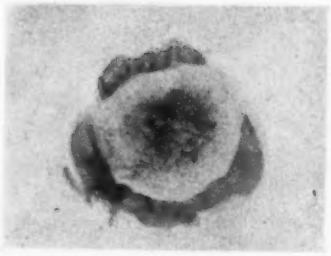

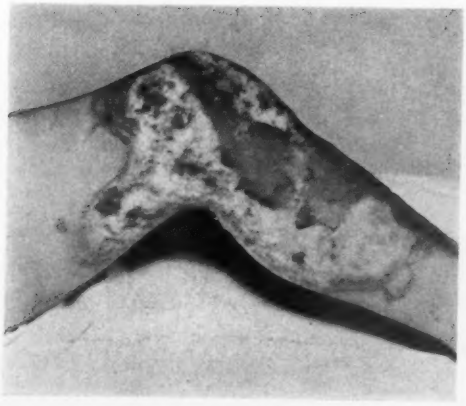

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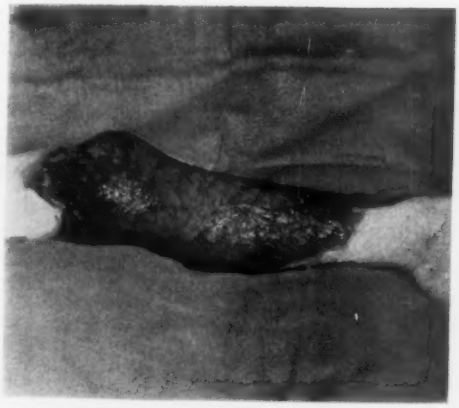

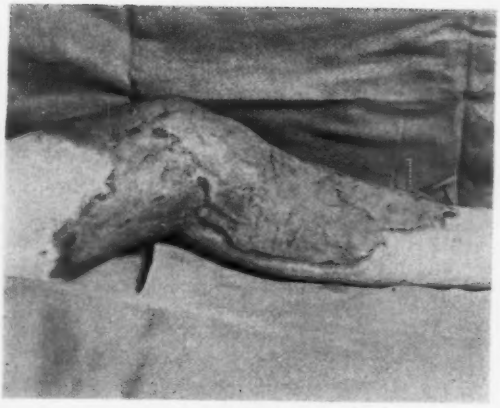

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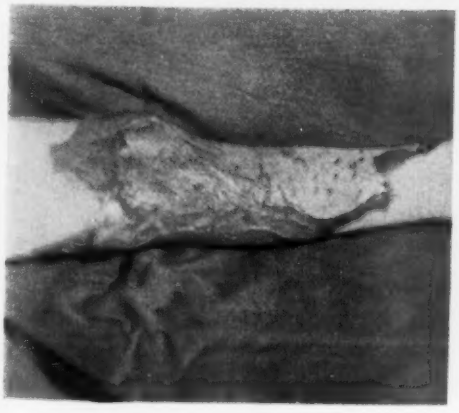

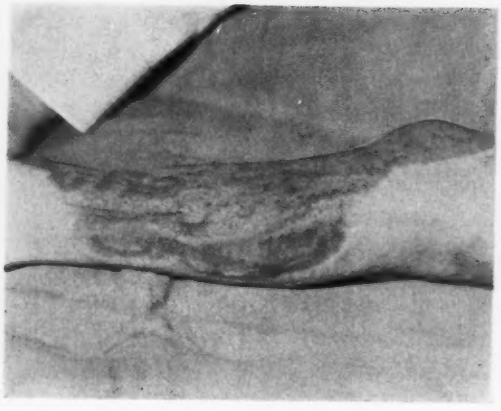

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otherwise, or loosely attached beneath its center (Fig. 7). In another 12 to 24 hours separation is complete, with the slough lying free in one piece.

It is clearly apparent, and is of special importance, that there is no evidence of digestion of the slough itself. It is similarly clear that the dermal strands at the periphery of the slough are last to separate, although they are markedly softened for many hours before separation is complete. The skin adjacent to the burn appears undamaged.

The resultant base is, grossly, pink subcutaneous tissue. Within 72 hours after burning, this base is unusually vascular and, histologically, exhibits evidence of early granulation tissue. The edges of the wound are sharp and clean, and are often tangential, as would be consistent with the more superficial damage at the very margins.

The full advantage of the rapid removal of the slough by this method is demonstrated when the wound is immediately grafted with skin. The pink, clean base evident after separation of the slough accepts a split-graft of skin immediately (Figs. 5 and 6). This regularly takes, and all or part of the wound may be successfully treated in this manner.

The problem of infection is thus resolved, and the full objective of treatment achieved even before the slough in the comparable control wound has completely separated.

The utility of this method of treatment of burns would be seriously reduced if with its use residual epidermal elements were necessarily destroyed. Such is not the case, however, for in those burns in which the damage extends only into the derma, but with preservation of the deeper epidermal elements, separation of the slough proceeds in such a manner as to permit epithelization from the intact islands of skin. Under these circumstances the cleavage plane develops within the derma, and the slough separates more slowly, often requiring an additional 48 hours over that necessary when the cleavage is beneath the derma.

Discussion.—Rapid removal of the slough can be achieved by the use of any of a large number of acids of various types incorporated in vehicles, the one necessary characteristic of which is a dominant water phase. It is important to recognize that this process is not a digestion of the slough, as is the case with the various enzymes previously employed. Instead of being broken up into fragments and dissolved, the slough separates as one or more large pieces. By this method the establishment of a plane of cleavage between dead and living tissue is accelerated, starting at the periphery, where the delimitation between the two occurs on the surface, and proceeding into the deeper tissues along the same boundary until the separation is complete and the slough so removed. This is apparently a speeding-up of the normal reaction to injury and, more specifically, that to dead tissue by means of which this is sequestrated and dislodged. The mechanism by which these acids bring about this acceleration requires further study.

To remove the slough in this manner, without damage to living tissue, requires not only the selection of the proper acid, but also careful and

accurate adjustment of the p_H and concentration of the acid chosen. When this is done, as shown by these experiments, not only can the dead tissue concerned in complete destruction of the skin be rapidly removed, but this can be accomplished without significant injury to the adjacent and viable epithelial cells. Moreover, when the separation of the slough is completed the base is living tissue, with an excellent blood supply, which will successfully and immediately take a skin graft, or if this is not done, healing of the wound by contracture and epithelization proceeds normally, as in a "cut-out" wound.

It is apparent that if these results can be obtained in the clinic, healing of the more severe burns may be markedly expedited by early grafting; and infection, scar tissue formation with contracture, and the general effects of a persisting open wound can be largely obviated.

The use of this method on man is being studied, but has not as yet been adequately tested, nor has a standardized procedure in all details been adopted. Until these have been done, its application for the purposes of treatment should be delayed.

SUMMARY

In the experimental laboratory it has been found that the normal development of a plane of cleavage between living and dead tissues can be markedly accelerated by the use of acids. With certain of the organic acids, in the proper concentration, and with a carefully and suitably adjusted p_H this can be accomplished without significant injury to viable tissues.

This makes it possible in the experimental animal to remove the slough resulting from a severe burn in 48–72 hours, and to employ immediate skin grafting for the closure of the wound.

The application of this method to man should wait upon further study and the development of proper methods of application.

The authors wish to express their appreciation to Dr. Philip B. Cowles of the Department of Immunology, Yale University, for his invaluable assistance in this study.

Acknowledgment is due to Dr. C. N. H. Long of the Department of Physiological Chemistry, for his valuable suggestions.

We wish to thank Mr. Howard Reynolds and Miss Mildred Konick for the photography.

REFERENCES

1 Cooper, G. R., Hodge, G. B., and Beard, J. W.: Enzymatic Débridement in the Local Treatment of Burns. Am. J. Dis. Child., **65**, 909–911, 1943.

2 Glasser, S. T.: A New Treatment for Sloughing Wounds. Am. J. Surg., **50**, 320–322, 1940.

3 Howes, E. L.: Progress Report No. 9. Committee on Medical Research of the Office of Scientific Research and Development. November 15, 1943.

A STUDY OF THE INTERRELATIONSHIP OF SALT SOLUTIONS, SERUM AND DEFIBRINATED BLOOD IN THE TREATMENT OF SEVERELY SCALDED, ANESTHETIZED DOGS*

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FLUID THERAPY is now recognized to be fundamental in the immediate treatment of burned or scalded man.[6, 11, 12] However, relatively little quantitative data are available concerning the individual physiologic effectiveness and the interrelationship of diverse repair salt solutions, cell-free blood components, and whole blood derivatives in the treatment of controlled thermal trauma. The purposes of these experiments are as follows: 1. To correlate body loads of various salt solutions and plasma with length of life and changes in other easily measurable physiologic constants that follow a scald; 2. to attempt a comparative evaluation of the relative rôles played by salt solutions, cell-free blood components, and whole blood in permitting immediate recovery from injury (74 to 100 hours following the trauma); 3. to correlate the gross and histologic, pathologic findings with the forms of therapy; and 4, to determine, if possible, whether or not any causal relationship exists between the type of therapy and the so-called "toxemic" stage of thermal injury.

METHODS

Seemingly healthy, adult mongrel dogs of both sexes were anesthetized solely with sodium evipal (1 methyl, 5 Δ' cyclohexenyl 5 methyl barbiturate). Fifty milligrams of a 5 per cent aqueous solution per kilogram body weight were injected intravenously as the initial dose; subsequently, a very light anesthesia was maintained for 14 to 20 hours by the administration of appropriate doses. Precautions were taken to provide a free air-way. Direct, mean, lateral arterial blood pressures were obtained in two-thirds of the experiments by femoral arterial puncture. The animals were scalded by immersion of two-thirds of the body in water at 85° C. for 30 seconds. The dogs were not clipped, since clipping was found to diminish the injury. Samples of venous blood were taken from the femoral, antecubital or jugular

* A preliminary report concerned mainly with purposes 1 and 2 (see page 1 of the text).

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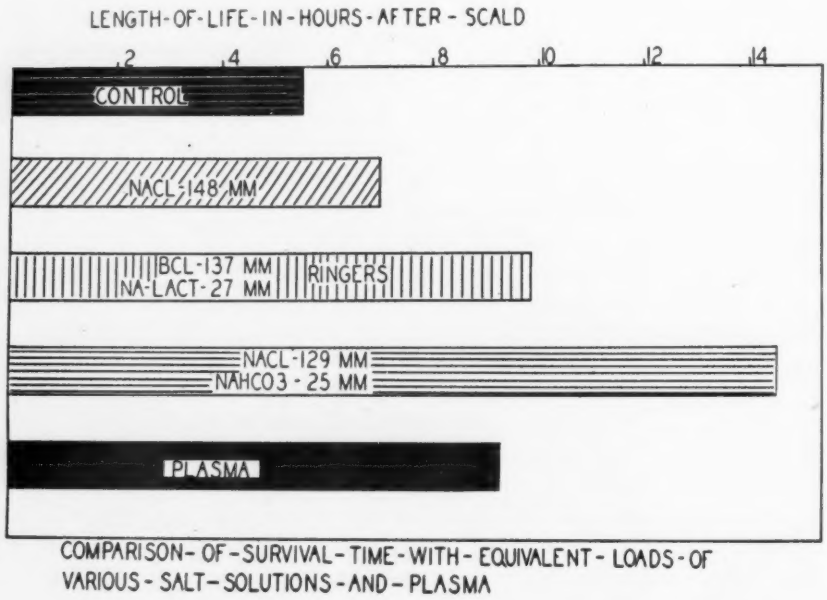
veins.† Heparin was used as the anticoagulant. The hematocrits were determined immediately by the capillary tube method. The specific gravities of whole blood and plasma were determined by the "falling-drop" method.[2] The plasma protein values, with the exception of the saline series, were corrected for hemoglobin; and micro-Kjeldahl checks[9] of the values of protein calculated from the specific gravities of the plasma were run. Hemoglobin was determined by the Evelyn method,[7] using the 20-c.mm. pipette of the falling-drop method. Urine was collected by a cystotomy tube or by a small urethral catheter inserted through an external urethrotomy in male animals, and by an indwelling flanged retention catheter in females.

RESULTS

Chart I and Table I show the mean survival time of the control group and of those animals loaded before the scald with physiologically equivalent amounts of (1) isotonic sodium chloride* (NaCl, 154 mM.); (2) Ringer's-

CHART I



COMPARISON-OF-SURVIVAL-TIME-WITH-EQUIVALENT-LOADS-OF VARIOUS-SALT-SOLUTIONS-AND-PLASMA

lactate (Ringer's, 137 mM. base + Na lactate, 27 mM.); (3) saline-bicarbonate (NaCl, 129mM. + $NaHCO_3$, 25mM.); and (4) citrated plasma.‡

The difference in survival time after the scald between the controls and the animals loaded with the physiologically acid, "isotonic" sodium chloride

† Simultaneously obtained samples from the jugular and femoral veins before and after the scald showed no significant difference.

* 50% of the volume of distribution of sodium thiocyanate (10% body weight).

‡ 50% of the volume of distribution of the dye T-1824 (2.5% body weight). Because of the severe citrate reactions which could be controlled only with injections of $CaCl_2$ solution i.v., serum was used in all subsequent experiments.

is insignificant (critical ratio = 0.9).‡ However, the animals loaded with Ringer's-lactate lived significantly longer than the controls and the saline group (critical ratio = 5.2), and those loaded with saline-bicarbonate lived longer than did all the other groups. NaCl-$NaHCO_3$ *vs.* controls (C.R. = 9.9); *vs.* saline (C.R. = 4.3); *vs.* Ringer's-lactate (C.R. = 6.5); and *vs.* citrated plasma (C.R. = 5.6).

TABLE I

SURVIVAL TIME OF CONTROLS AND DOGS LOADED BEFORE SCALD

Treatment	No. of Dogs	Mean Survival Time		Standard Error Minutes	Standard Deviation Minutes	Critical Ratio*
		Hours	Minutes			
Controls	7	5	21	±31	81	
0.9% NaCl, 10% body weight*	5	6	50	±94	210	0.9
NaCl—Na. lact., 10% body weight*	7	9	37	±38	92	5.2
Citrated plasma, 2.5% body weight†	4	9	5	±32	64	5.1
NaCl—NaHCO , 10% body weight*	4	14	12	±44	88	9.9

* 50% volume of distribution of sodium thiocyanate.
† 50% volume of distribution of the dye T—1824.
± A critical ratio of 3.3 or more indicates a true difference in 999 cases in 1000.

TABLE II

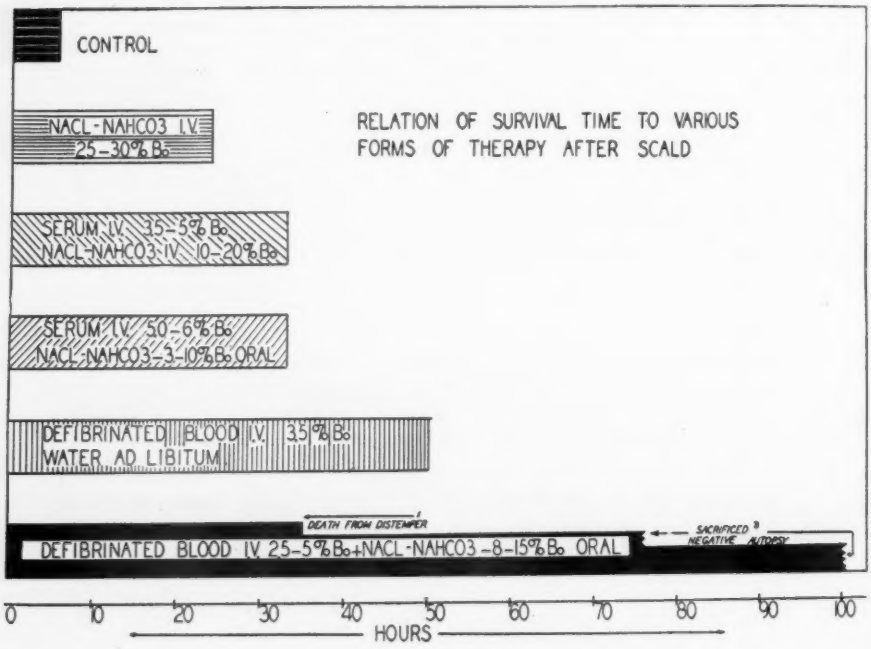
Animal No.	Immediate Treatment During First 24 Hours, Per Cent, Body Weight					Survival Time Hours	Cause of Death
	Blood	Serum	NaCl NaHCO	Route, Fluid	H_2O Ad Lib.		
39	0	0	25	i.v.	0	24	Shock, pulmonary congestion.
40	0	0	30	i.v.	0	25	Shock.
41	0	0	30	i.v.	0	25	Shock.
43	0	0	12	i.v.	0	3	Acute cardiac failure.
42	0	5.0	28	i.v.	0	52	Pulmonary congestion.
44	0	3.5	28	i.v.	0	23	Pulmonary edema and congestion.
45	0	3.8	23	i.v.	0	31	Pulmonary edema and congestion.
46	0	4.5	15	i.v.	0	29	Acute pulmonary edema.
48	0	1.6	5	i.v.	0	28	Shock.
64	0	5.0	6	oral	0	10	Pulmonary edema.
65	0	5.0	3	oral	0	20	Pulmonary edema.
66	0	6.0	5	oral	0	70	Pulmonary edema and pneumonia.
60	3.6	0	0	—	5.5	50	Brain and pulmonary edema.
61	3.4	0	0	—	10.0	92	Brain edema, pulmonary congestion.
62	3.5	0	0	—	5.0	34	Brain edema.
63	3.5	0	0	—	0	19	Shock, pulmonary congestion.
56	2.5	0	8	oral	0	35	Distemper.
57	2.2	0	15	oral	0	76	Sacrificed, negative autopsy.
58	2.7	0	11	oral	0	100	Sacrificed, negative autopsy.
59	5.1	0	13	oral	0	100	Sacrificed, negative autopsy.

Following the "load" series of experiments, a comparative study of therapy was undertaken. Chart II shows the effects of various forms of therapy upon the survival time. The relation of the various forms of therapy to survival and the causes of death based upon the gross pathologic findings are shown in Table II.

† Critical ratios of 3.3, or more, are significant.

Discussion.—In order to apply the principles of bio-assay to the study of the relative effectiveness of various salt and blood elements in treating small series of scalded animals, it is theoretically necessary that the extent and the depth of the injury should be of such a degree that death will occur in all the animals of all series, excepting one. Upon that basis, an injury

Chart II

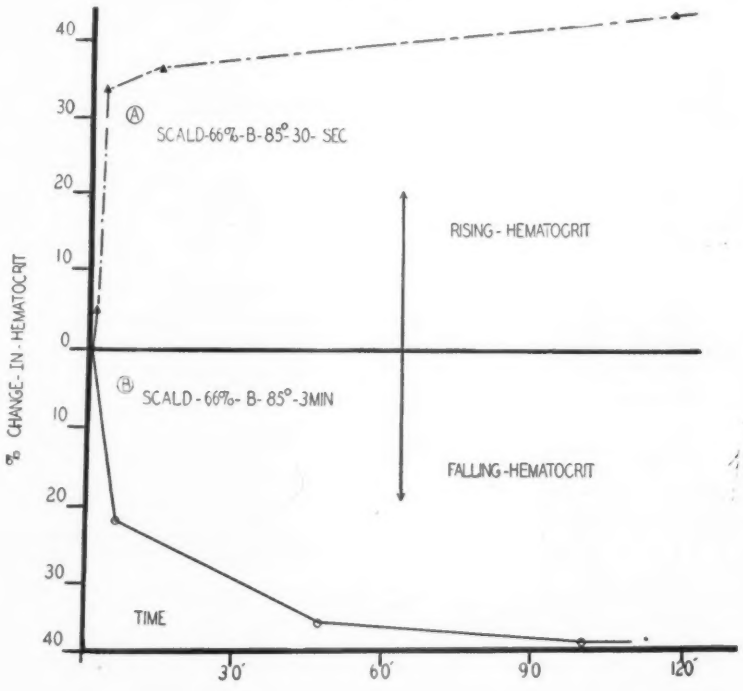


that killed within three hours would be more desirable than one that killed within six hours. However, although a scald produced by the immersion of two-thirds of the body surface in water at 85° C. for three minutes kills within three hours, it produces a picture which is unlike the majority of thermal injuries seen in man (Chart III). Compare the hematocrit change A (85° C. for 30") with B (85° C. for 3'). Therefore, the scald produced by water at 85° for 30 seconds, although it killed in a little over five hours, was chosen as the means of producing a relatively constant thermal trauma against which the various solutions were assayed.

The series of experiments in which the test solutions were injected before the scald in equivalent physiologic amounts show that a positive load of the physiologically acid solution of isotonic sodium chloride has practically no propensity for prolonging life after a severe scald. A load of Ringer's solution to which sodium lactate has been added to make a fluid osmotically equivalent to the isotonic salt solution significantly increased the length of life. Was it the addition of the cations Mg. and K. or the addition of the

anion HCO_3^- that effected the change? The increased survival time in the next series of experiments (preburn loading with sodium chloride-sodium bicarbonate) shows that if the cations exert any effect it is small when compared to the anion HCO_3^- effect (the HCO_3^- equivalency of the NaCl-$NaHCO_3$ solution is physiologically double that of the Ringer's-lactate solution).

CHART III



Loading with plasma was surprisingly ineffective: From one-fifth to one-half of the protein that was injected disappeared from the blood stream within the hour and an half which was allowed to elapse between the completion of the injection and the scald.

No experiments were conducted using M/6 sodium lactate as the preburn load because of its adverse effects upon the acid-base equilibrium and its obviously extensive constitutional difference from interstitial fluid.* The administration of this solution in large amounts would make the transfusion of citrated plasma or blood extremely hazardous and, if renal function was depressed, would effect alterations in the relationship between interstitial and cell fluid that must be considered as physiologically undesirable.

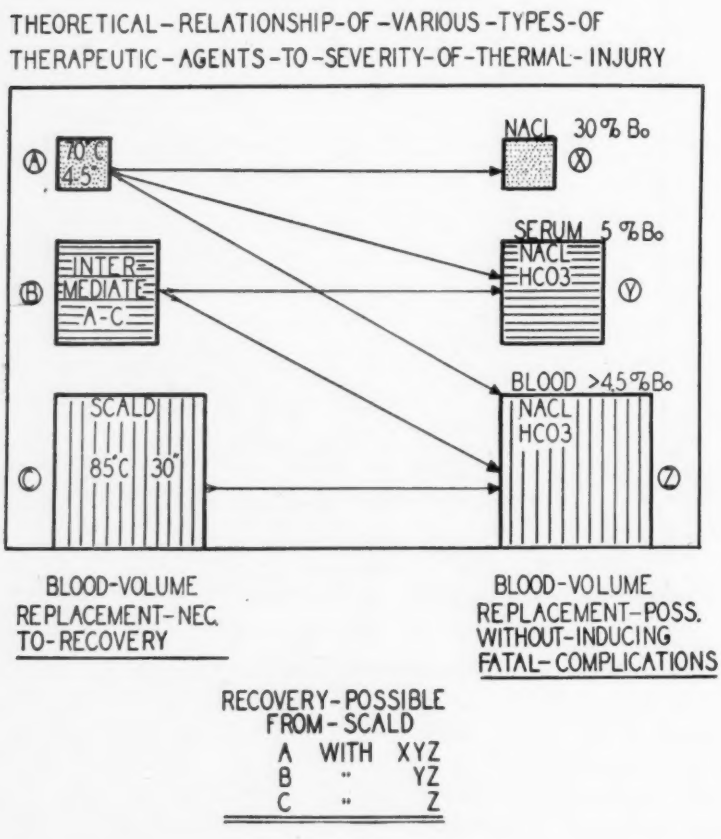
The significant superiority of saline-bicarbonate as a repair solution in thermal injury is somewhat surprising in view of prevalent opinion,[6] and other experimental work.[10] However, it is in agreement with general

* Unpublished data.

physiologic knowledge that the more nearly a solution approximates the composition and reaction of the normal body fluids, the more satisfactory it is for studying living tissues *in vitro*.

The results of the second series of experiments show that saline-bicarbonate, when administered intravenously after the scald to 30 per cent of body weight, prolonged life but did not prevent an hypotensive death. The injections of these large amounts of saline-bicarbonate were attended by

CHART IV



profound, persistent, and disproportionally great depressions of the plasma proteins and the rapid development of massive subcutaneous edema in the scalded area. Saline-bicarbonate does not differ from isotonic, intravenous saline in this respect.[3]

The intravenous injection of both saline-bicarbonate and serum either killed (by inducing acute pulmonary edema and pulmonary congestion), or the amounts given were inadequate. In other words, any amount of both fluids that was less than that which produced pulmonary or cardiac complications would not prevent death from "shock." As a result of observations

made during the saline-bicarbonate and the saline-bicarbonate-serum series, it was decided that the only "safe" way to give salt solution during the acute stages of thermal injury was *via* a route whereby the rate of entrance of the solution into the blood stream was controlled by the animal, namely, by stomach, by rectum or subcutaneously. The saline-bicarbonate solution in all the later experiments was given by stomach catheter (Table II). Absorption of saline-bicarbonate to the extent of 10 to 13.5 per cent of body weight usually took place within 12 hours.

The three animals that were treated with serum by vein (5 per cent of body weight within 13 hours) and sodium chloride-bicarbonate solution by stomach tube died of pulmonary edema, two within 24 hours and one within 70 hours. The latter showed clinical signs of pulmonary edema throughout her life, and at death the edema had progressed to an extensive hepatization of four-fifths of both lungs.

Defibrinated whole blood without saline-bicarbonate effected temporary recovery, but all the animals in the series died within 70 hours of the scald. This agrees with the observations of Williams, Eghart and Trusler.[13] Twenty-four hours after the scald three animals out of four had fully recovered from the anesthesia. They were walking easily about their cages without signs of pain, and they drank large amounts of water when it was given to them. Shortly after drinking the water (2 to 20 minutes) they began to vomit and to have a bloody diarrhea. Thereafter, they continued to drink, to vomit and to defecate until too weak to drink. Fibrillary twitching of all muscle groups appeared when they were unable to get up, and they died suddenly, howling and in convulsions. After death their brains bulged over the edges of the skulls after removal of a bone flap, and fluid dripped from the cut surface of the cerebrum. The general appearance and behavior of these animals could be called "toxemic." These observations lead us to believe that in the absence of infection, the "toxemic" stage of burns may be largely the result of cellular "overhydration" associated with hypotonicity of extracellular fluid in the uninjured portions of the body. Indirect support for this concept is provided by the lack of these signs within a period of 100 hours (longest time elapsed before sacrifice) in animals treated with blood and oral isotonic saline-bicarbonate during the first 24 hours and hypotonic saline-bicarbonate, in as large amounts as the animals would drink, during the second 24 hours (Table II).

The only form of therapy that is capable of carrying these scalded animals (two-thirds body surface, 85° C. for 30″) through the "shock" period *without inducing physiologic changes that may in themselves result in death* in less than 100 hours (four days) is a combination of *defibrinated whole blood* intravenously and sodium chloride-sodium bicarbonate by mouth (Table II).

We have no assurance that citrated or heparinized blood will be as effective as defibrinated blood. The work of Ivy,[8] and Graham,[5] suggests that citrated blood may be found to be inferior and may even be detrimental.

Heparinized blood, should it act similarly to heparinized plasma, will increase the escape of red cells into the area of injury.*

It has been interesting to find that an hematocrit of 75 to 80 per cent that was maintained for 8 to 10 hours, in scalded animals, given massive transfusions of defibrinated blood, is compatible with life, provided that sodium chloride-bicarbonate is also given by stomach. Hence, even the hemoconcentration of severe thermal injury does not contraindicate the transfusion of whole blood, if the general physiologic state of the animal requires it. No gross cardiac or circulatory abnormalities were associated with the high hematocrit, and no significant, gross pulmonary, hepatic, renal, cerebral, splenic, or mesenteric infarcts were seen at autopsy following sacrifice of the animals. These observations substantiate Darrow's[6] comments regarding the transfusion of whole blood in the treatment of the shock of burns, and agree with those made by the British Army Medical Corps during the Libyan Campaign. (Col. F. G. Gillespie, personal communication.)

The amount of saline-bicarbonate, in conjunction with defibrinated blood, that is needed to balance the negative load of interstitial fluid imposed upon the uninjured portions of the body by the injury cannot be clearly defined. By using multiple indirect methods that will be described in a separate article, the negative loads of interstitial fluid imposed by the scald in these series of experiments was from 3 to 7 per cent of body weight within 30 minutes after the scald and from 10 to 18 per cent of body weight within 24 hours after the scald. In general, the negative load of interstitial fluid is directly proportional to the inevitable, although variable edema.

It must be remembered that the washing-out of protein from the blood into the scalded tissues and the very rapidly developing and massive edema that attend the intravenous administration of sodium chloride or saline-bicarbonate solutions during the first 24 hours after injury, make the intravenous route unsuitable for the reduction of the acute negative interstitial fluid load. In fact, it is theoretically possible that any salt solution given intravenously immediately following a scald may actually accentuate rather than diminish the physiologically functional negative load of interstitial fluid.

The major clinical generalization regarding the therapy of thermal injuries that can be drawn from these experiments has been stated very clearly by Allen,[1] namely: "Ever since the first introduction of the colloid concept, physicians and experimenters have concentrated on treating the blood instead of the patient."

In general, if these experimental observations are valid for all mammals, the therapy of a thermal injury should be directed toward two primary goals: First, blood volume must be maintained at a level that will prevent death from "shock." In the case of a relatively minor injury, this can be done with interstitial fluid alone,[10] serum alone,[10] and presumably with whole blood alone. However, in the case of a severe injury such as obtained in our experiments, defibrinated blood is the only substance tested that is capable

* Unpublished data.

of maintaining a blood volume compatible with life without inducing lethal complications. Chart IV is a theoretical diagram illustrating the relationship of therapeutic measures to the constitutional severity of the injury. Second, the negative load of interstitial fluid induced by the injury must be reduced preferably to zero. During the acute stage of the injury, this can be done most safely by administering a salt solution which approximates normal interstitial fluid by a route other than the intravenous.

CONCLUSIONS

1. Saline-bicarbonate solution is more effective than Ringer's-lactate solution, and Ringer's-lactate solution is more effective than "isotonic" sodium chloride solution in prolonging life of anesthetized dogs when 10 per cent of body weight of these solutions is given intravenously before the animals are scalded (two-thirds body surface at 85° C. for 30 seconds). The presence of the bicarbonate ion or the potential bicarbonate ion in the lactate solution appears to be responsible for the superiority of the Ringer's-lactate and the saline-bicarbonate solutions.

2. The combination of massive transfusions of defibrinated blood and saline-bicarbonate solution by stomach was the only form of therapy employed that prevented shock without inducing complications that were incompatible with life.

3. The other forms of therapy employed, namely: (1) Saline-bicarbonate, i.v.; (2) saline-bicarbonate i.v. and serum i.v.; (3) serum i.v. and saline-bicarbonate by stomach; and (4) defibrinated blood i.v. and water *ad libitum,* prolonged life and in a number of instances prevented shock. But all the animals that did not die of shock during the first 24 hours died later of complications that seemed to be related to the therapy rather than to the trauma.

4. An hematocrit of 80 to 85 per cent does not prohibit the use of transfusions of whole blood.

The authors wish to express their indebtedness to Dr. Kenneth N. Campbell who prepared the tables and graphs, and to Mr. William Troy whose technical assistance has been deeply appreciated.

BIBLIOGRAPHY

[1] Allen, F. M.: Theory and Therapy of Shock. Am. Jour. Surg., **61,** 82, 1943.

[2] Barbour, H. G., and Hamilton, W. F.: The Falling-Drop Method for Determining Specific Gravity. Jour. Biol. Chem., **69,** 625, 1926.

[3] Beard, J. W., and Blalock, A.: Intravenous Injections: A Study of the Composition of the Blood during Continuous Trauma to the Intestines when No Fluid is Injected and when Fluid is Injected Continuously. Jour. Clin. Invest., **11,** 249, 1932.

[4] Blalock, A., and Beard, J. W.: The Effects on the Composition of the Blood of Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection. Jour. Clin. Invest., **11,** 311, 1932.

[5] Bruneau, J., and Graham, E. A.: A Caution against Too Liberal Use of Citrated Blood in Transfusions. Arch. Surg., **47,** 319, 1943.

[6] Darrow, D. C.: The Treatment of Dehydration, Acidosis and Alkalosis. Jour. Am. Med. Assoc., **114**, 655, 1940.

[7] Evelyn, K. A.: The Determination of Oxyhemoglobin. Jour. Biol. Chem., **115**, 63, 1936.

[8] Ivy, A. C.: Greengard, H., Stein, I. F., Grodins, F. S., and Dutton, D. F.: The Effects of Various Blood Substitutes in Resuscitation after an Otherwise Fatal Hemorrhage. Surg. Gynec. and Obst., **76**, 85, 1943.

[9] Pregl, F.: Die quantative organische Microanalyze. Berlin, 1923. 2nd Edition.

[10] Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock. Pub. Health Rep., **57**, 1923, 1942.

[11] Underhill, F. P., Carrington, G. L., Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment. Arch. Int. Med., **32**, 31, 1923.

[12] Underhill, F. P.: The Significance of Anhydremia in Extensive Superficial Burns. Jour. Am. Med. Assoc., **95**, 852, 1930.

[13] Williams, H. S., Eghart, H. L., and Trusler, H. M. Burn Shock. Jour. Am. Med. Assoc., **113**, 2207, 1939.

[14] Adolph, E. F.: Physiologic Regulations. Science Press. Lancaster, 1943.*

[15] Drinker, C. K., and Yoffey, J. M.: Harvard University Monograph in Medicine and Public Health. No. 2 Cambridge, 1941.*

[16] Eichelberger, L., and Hastings, A. B.: III—The Exchange of Salt and Water between Muscle and Blood. Jour. Biol. Chem., **118**, 205, 1937.*

[17] Hastings, A. B., and Eichelberger, L.: The Effect of an Increase in Total Body Water produced by the Intravenous Injection of Isotonic Salt Solutions. Jour. Biol. Chem., **117**, 73, 1937.*

[18] Peters, J. P.: Body Water. Springfield, 1935.*

* There is no specific reference in the text to these publications, but because of their influence upon the course of the experiments they are included in the bibliography.

A COMPARISON OF VARIOUS TYPES OF LOCAL TREATMENT IN A CONTROLLED SERIES OF EXPERIMENTAL BURNS IN HUMAN VOLUNTEERS*

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THE INTENSIVE STUDIES which have been carried out in recent years have led to a fair degree of standardization of certain aspects of the care of burns, notably in the prevention and treatment of shock and also of the severe metabolic derangements which may appear later in the course. A greater degree of confusion exists, however, with regard to the local treatment, for, here, certain quite obvious factors have prevented accurate comparisons of even the most promising of the very considerable number of methods which have been brought out or reemphasized from time to time. Thus, it is obvious that no two individual burns, nor any two series, unless both include large numbers of cases, are exactly comparable due to discrepancies in size and severity of the burns and wide variations in age, sex and condition of nutrition in the patients. Nor do experiments in animals offer a better solution of the problem since the local reaction to heat sufficient to cause a burn differs somewhat from species to species and in none does the vesiculation appear which is so prominent a feature of second degree burns in the human.

Certain attempts have already been made to obviate this difficulty by using various portions of a burned area or different regions of the body in a single patient for comparing results of different types of local treatment. Such a method is obviously quite crude when one considers variations in depth of the burn as well as the definite, though small, differences in normal healing rate in various parts of the body. In 1943, Cannon and Cope[1] suggested the use of Thiersch graft donor sites which could be divided into parts for testing two or more agents on the same lesion. While their results indicate that this is a useful method for comparing substances of different modes of action such as a bland ointment and an escharotic, it is subject to certain drawbacks. Thus, it is difficult to cut a graft of exactly the same thickness throughout. And, perhaps, more important is the fact that local agents applied at one limit of such an area may exert an influence to some degree on the neighboring regions or even on the extremes. Finally, although histologically akin, a split-thickness donor area does not simulate a burn exactly because of the different mechanics producing the tissue damage.

We have, therefore, produced bilateral, symmetrical burns in human volunteers for comparative studies of various agents, using a simple apparatus

* Read before The American Surgical Association, May 3–4, 1944, Chicago, Ill.

consisting of a hollow metal plate of almost exactly ten square centimeters area through which live steam is passed. When such a device, of constant temperature and area, is applied to symmetrical points on the anterior aspect of the thighs for the same length of time, as determined by an electric timer by which tenths of seconds were easily measured, we believe the resulting burns should be very nearly alike in every way, including depth. As will be noted later, also, the burns were very much alike from individual to individual but it was early found necessary to vary the time slightly in the case of women since the few who were included sustained deeper burns than were produced by application of equal duration in males. Cornell University Medical students made up most of the volunteers, and ranged in age from 21 to 26 years.

As proved by biopsy, the fluorescein test,[2] and the nature of the subsequent healing process of uncomplicated lesions, these areas were deep second degree burns, epithelization being accomplished from viable epithelium remaining in hair follicles, sweat ducts and sebaceous glands. Without fail, all lesions showed vesiculation in 24 hours (Fig. 1). It should be mentioned that skin areas to be burned were routinely prepared with iodine and alcohol save in a few instances where the areas were purposely left in a normal state of contamination.

For the first 24 hours following the production of these lesions dry sterile gauze was used as a covering, secured by adhesive tape, completely closing the areas, and the subjects were ambulatory throughout the subsequent course of therapy. The 24-hour delay before definitive therapy was chosen in order to simulate accidental burns, since these are frequently seen after some time had elapsed.

EXPERIMENTS

Following removal of the initial dressing, all vesicles were opened using sterile technic, and the areas were débrided in the majority of instances. Routine cultures were taken at this time. One burn was then selected at random for definitive therapy with one agent, and the contralateral area was used as a control, a different therapeutic preparation being employed. A total of 82 burns in 41 subjects were thus available for study.

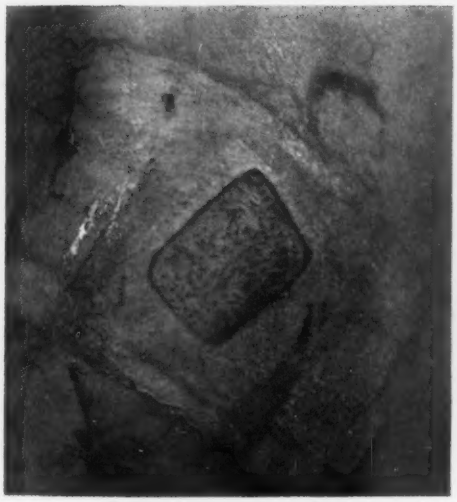
The effect upon healing of 12 substances of which three were escharotics, was compared and the observations made on the rate and mode of healing and the final result. The end-point was arbitrarily chosen as the time at which epithelium covered the entire area.

Sulfafilm.—In the majority of cases a film* was employed as a control as it is the therapy of choice for second degree burns in this clinic and we are interested in obtaining objective comparison with other more common types of local burn treatment. The film used was essentially of two types which we designated as "new" and "old" films. Both were made of a methyl cellu-

* A generous supply of sulfafilm was furnished by the manufacturers, Wallace and Tiernan Products, Inc., Belleville, New Jersey.

FIG. 1

FIG. 2



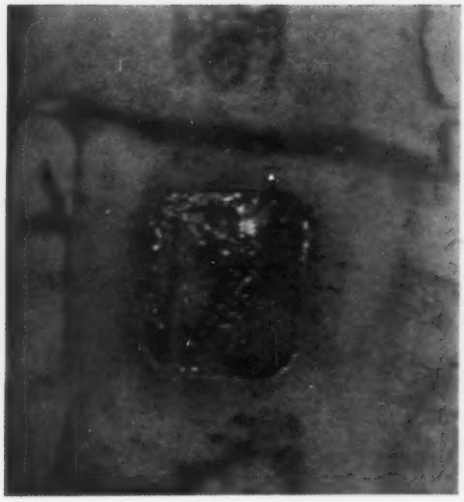


FIG. 3

FIG. 4

FIG. 1.—Bilateral, symmetrical blisters 24 hours following burns. Note the similarity between the two sides.

FIG. 2.—Tannic acid eschar intact, showing swelling, redness and inflammatory reaction surrounding lesion six days after application. Patient was complaining bitterly of local pain and had inguinal adenopathy.

FIG. 3.—Contralateral burn in same patient as shown in Figure 2. Note absence of reaction.

FIG. 4.—Tannic eschar removed on 12th day with no healing evident. Granulations are prominent, suggesting conversion to deeper burn. Inflammatory reaction is still present around the lesion.

FIG. 5

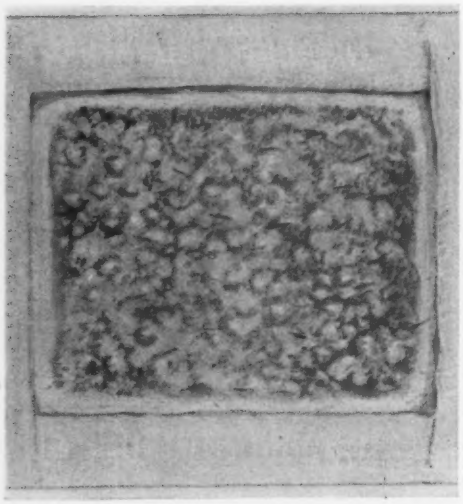
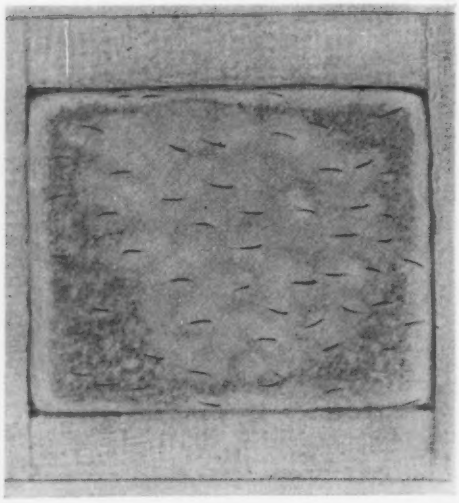


FIG. 6



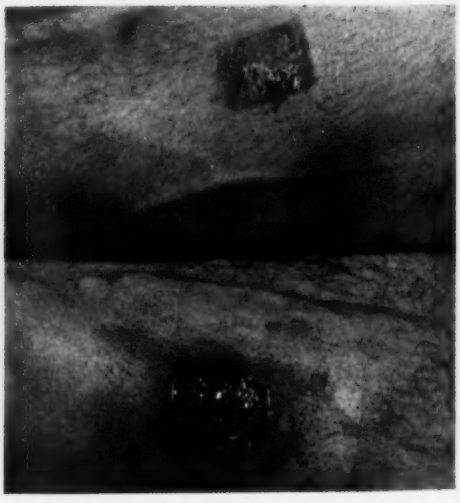


FIG. 7

FIG. 8

FIG. 5.—Boric ointment-treated lesion on 6th day. Note prominence of epithelial islands with surrounding granulations.

FIG. 6.—Sulfonamide film-treated control in same patient shown in Figure 5. Note coalescence of epithelium as compared to discreet islands in boric-treated lesion.

FIG. 7.—Triple dye eschar intact on 7th day with little surrounding reaction. Control (sulfonamide film) healed.

FIG. 8.—Same patient as in Figure 7 showing conversion to deeper burn after painful removal of triple dye on the 12th day. Control (sulfonamide film) healed five days before.

lose, triethanolamine base into which either buffered sulfanilamide 10 per cent was impregnated or a combination of the former in a concentration 10 per cent and sulfacetamide 15 per cent, making a total of 3 mg. of sulfonamide per square centimeter of film. In principle, the film was a "preformed, bacteriostatic eschar," liberating sulfonamide locally on exposure to aqueous fluid. It was transparent, allowing visualization of the underlying surface without removal, pliable, 0.004 inches thick; the film was buffered in order to maintain the surrounding media at a p_H of approximately 8.5. This agent was applied in one or more layers to 42 lesions, the opposite side being treated with one of the substances mentioned below. The average healing time for all uncomplicated second degree lesions treated with film was 9.6 days, but certain aspects of this figure require explanation which will be presented later. Not included in the average are four areas similarly treated, two of which were on female subjects who sustained considerably deeper burns than the males because of the different skin thickness. One lesion was inoculated with *hemolytic Staphylococcus aureus* (in an overwhelming dose) and it became grossly infected within 48 hours, the subject having chills, fever and malaise. Hot wet dressings were applied and subsequent bland ointments. The fourth was one of three subjects who had received two consecutive burns on both thighs. Following application of the film for the second time he developed a severe dermatitis, about which more will be said later.

Tannic Acid.—Tannic acid was applied to five areas in the form of tannoid ointment* which was left on for 48 hours, at which time a characteristic firm, leathery eschar was present. In two additional instances a solution containing five per cent tannic acid and five per cent silver nitrate was used. This was applied continually until a firm eschar was formed.

TABLE I

HEALING TIME WITH TANNIC ACID PREPARATIONS AND CONTROLS

	Tannoid	Control (Sulfafilm)
No. 1	27 days	14 days
No. 2	24 days	13 days
No. 3	22 days	13 days
No. 4	16 days	11 days
No. 5	14 days	7 days
	Tannic Acid—Silver Nitrate	**Control (Sulfafilm)**
No. 1a	24 days	8 days
No. 2a	21 days	11 days

In Nos. 1, 2, 3, 5, 1a and 2a there was characteristic reddening, tenderness, swelling and inguinal adenopathy, with gross infection present under the eschar in No. 1 and No. 5. The eschar was left intact in most instances for about nine days, but in one case it remained for 16 days, at which time

* The qualitative formula was tragacanth USP grade (extra select); glycerin USP, methiolate solution 1:1000, 95 per cent alcohol, distilled water and tannic acid to 5 per cent of whole.

the lesion was healed (No. 4). In all others granulation tissue was present, but the areas subsequently healed by epithelization from scattered foci of glands and ducts. All subjects complained bitterly of these areas in contrast to the controls (Figs. 2, 3, and 4).

Boric Acid Ointment.—In five cases ten per cent boric acid ointment was used as definitive therapy, being applied to the débrided burns in mesh gauze and covered with more gauze as pressure dressings. Healing time of the lesions thus treated and those of the controls are shown in Table II.

TABLE II

HEALING TIME WITH BORIC OINTMENT AND CONTROLS

	Boric Acid Ointment	Control (Sulfafilm)
No. 1	26 days	16 days
No. 2	16 days	14 days
No. 3	18 days	14 days
No. 4	21 days	14 days
No. 5	15 days	11 days

Subjects on whom boric acid ointment was used reacted favorably: they had no pain, little reaction, and could not distinguish symptomatically between the two sides.

Boric Acid Ointment—Sulfadiazine by Mouth.—Five areas were also treated with boric acid ointment in the same manner as that described above, but during the full course of treatment the subjects were given sulfadiazine, 1 Gm. five times a day by mouth, with adjuvant alkali therapy of 2.5 Gm. of sodium bicarbonate with each dose.[3] All had satisfactory sulfa levels throughout treatment (from 5.5–8.0 mg. %) and none had toxic reactions to the drug save headache in three cases.

TABLE III

HEALING TIME WITH BORIC OINTMENT AND CONTROLS

	Boric Acid Ointment Sulfadiazine by Mouth	Control (Sulfafilm)
No. 1	13 days	8 days
No. 2	12 days	7 days
No. 3	7 days	7 days
No. 4	8 days	7 days
No. 5	9 days	7 days

In this group, although there was a similarity in healing time of contralateral sides, there was a rather noticeable difference in the character of epithelial regeneration. As has been said, in all burns healing was accomplished by the growth and spread of discrete epithelial islands from hair follicles, ducts and glands. If the ointment-treated side was compared at a near-healing point with the film-treated control, it was noted that in the latter the epithelial "mushrooms" were more flattened, more coalescent, and looked more like mature skin than did that of the ointment-treated side where the islands of epithelium appeared as discrete, shiny noncontiguous rests (Figs. 5 and 6). The resultant scar of the latter also required a longer time to assume the characteristics of normal skin.

The explanation of this difference is somewhat obscure. We believe that the mechanical feature of the glass-like film in contact with the sprouting epithelium under some pressure may exert a flattening influence causing more rapid coalescence among the islands, whereas, in the other instance the new epithelial buds may protrude between the meshes of the gauze. It is interesting to note in this connection that the size of the mesh spaces and the epithelial islands nearly coincided. The influence which sulfadiazine may have played in shortening the healing time of boric ointment treated lesions will be discussed later.

Triple Dye.—In four instances a second type of escharotic, triple dye,* was used. This was applied to the débrided burn areas with cotton swabs until a firm light eschar was obtained. On the whole, such eschars were tolerated better than those obtained with tannic acid, there being very little reaction around the lesions, and no subjective symptoms save continued apprehension on the part of the subject as to whether "infection was developing," especially after the control areas were healed (Fig. 7). The eschars were removed, *with difficulty,* by sharp dissection, and with marked pain in from 19 to 28 days (Fig. 8). In one case the eschar was left to slough itself, which it did in 31 days, following three or four days of baths. At this time the burn in question was 90 per cent healed, requiring an additional seven days. Healing time for these experiments with their control in the same individual is shown in Table IV.

TABLE IV

HEALING TIME WITH TRIPLE DYE AND CONTROL

	Triple Dye	Control (Sulfafilm)
No. 1	29 days	8 days
No. 2	31 days	9 days
No. 3	45 days	11 days
No. 4	38 days	8 days

At first glance, it will appear that the healing time of the dye treated lesions was longer than that of tannic acid preparations. It should be stated, however, that because of the reaction, tenderness and general distaste for the tannic eschar, they were removed earlier than those of the better tolerated triple dye. The lesions in all instances of escharotic treatment which were not healed on removal of the eschar were treated with bland ointments or adult animal tissue extract[4] until finally epithelized.

Control Film.—Since we were desirous of knowing what part, if any, the presence of sulfonamides in the plastic film played in the apparent efficacy of this type of treatment, five areas were treated with a control film similar in substance to sulfafilm but without sulfonamide present. Healing times for these lesions are shown in Table V.

* Aniline gentian violet, 2%; brilliant cresyl green, 1%; neutral acriflavine, 0.1% in 70% alcohol.

TABLE V

HEALING TIME WITH FILM CONTAINING NO SULFONAMIDE

	Film without Sulfonamide	Control (Sulfafilm)
No. 1	15 days	10 days
No. 2	15 days	11 days
No. 3	10 days	7 days
No. 4	11 days	10 days
No. 5	17 days	12 days

Of interest in the above comparison is the fact that although on original culture both the treated and control areas showed no growth of organisms, in three of the five areas which were tested with the blank film positive cultures subsequently developed, whereas, no positive cultures were obtained from the sulfafilm-treated lesions. It is possible that this may be responsible for the delayed healing time, for in two instances frank infection occurred under the film without sulfonamide.

Vaselined Gauze.—Four areas were treated with vaselined gauze and pressure without any sulfonamide by mouth. Comparison is shown in Table VI.

TABLE VI

HEALING TIME WITH VASELINED GAUZE AND CONTROLS

	Vaselined Gauze	Control (Sulfafilm)
No. 1	26 days	11 days
No. 2	7 days	7 days
No. 3	8 days	8 days
No. 4	20 days	7 days

It should be noted again that although all areas treated with vaselined gauze were negative on original culture, Nos. 1 and 4 subsequently became infected, both with *hemolyticus Staphylococcus aureus,* and treatment with the neutral petrolatum had to be discontinued. In two instances no infection occurred, and the healing time compared favorably with that of the control.

Triethanolamine-Sulfadiazine with Methocel.—This preparation was applied to one area with the control in the same subject being sulfafilm. Healing times were 21 days and 12 days, respectively. Although estimated to be an escharotic of sorts, the triethanolamine-sulfadiazine-methocel preparation failed to produce an eschar in 48 hours.

Penicillin Ointment.—An ointment of penicillin containing 150 Oxford units per gram was used in one case. The area was not dressed for five days, at which time because of extreme burning, pain and itching the dressing was opened. The area was inflamed, pitted with tender granulations, and showed isolated areas of infection. Further, the surrounding normal skin was excoriated, ulcerated and tender. Further treatment with this method was discontinued. Subsequent healing time of the converted lesion was 34 days. The control area (sulfafilm) was healed in eight days.

Fibrin Film.—In two instances a plastic film containing human fibrinogen was used. In one of these sulfadiazine was present and in the other there was no sulfonamide (Table VII).

TABLE VII

HEALING TIME IN DAYS

Fibrin Film with Sulfadiazine	Control (Sulfafilm)
7	7
Fibrin Film without Sulfadiazine	Control (Sulfafilm)
18–20	11

Gross infection occurred under the fibrin film which did not contain sulfadiazine.

Sulfadiazine-Gelatin.—A preparation of sulfadiazine containing both soluble sodium salt and insoluble sulfadiazine dissolved and suspended in a gelatin base was used in three cases. The resultant mixture was semisolid at room temperature, but on heating became semiliquid. This was painted on the burn area in three cases. Healing times were 11, 7 and 9 days, respectively, as compared to sulfafilm-treated control areas which healed in 13, 8 and 11 days. As a practical burn treatment, however, technical difficulties were encountered. A rubbery eschar was obtained in 20 to 30 minutes after application, but this partially dissolved when serum from the burned area contacted the water-soluble gelatin. For the small areas so treated this was overcome by sealing the gelatin eschar with cellophane and collodion. The resultant dressing remained intact for the time necessary for healing. Such a dressing, however, would be technically impractical for burns involving large areas of the body.

COMMENT

Aside from the comparison between bilateral burns in the same individual, some interesting observations were made in the burns of different subjects which were treated by a similar agent. Naturally, at the beginning of a series of burns in human volunteers the authors were consciously aware of the undesirability of encountering untoward complications, particularly as represented by uncontrolled infection which might require such treatment as would interfere with the usual medical student routine. Further, the cosmetic end result of these lesions was advertised to the subjects as minimal scar formation. Consequently, we were admittedly overzealous at first in our dressing routine, the lesions which were progressing satisfactorily frequently being redressed several times. As more confidence was gained in our control method, and in some of the experimental treatments, dressings became fewer, and in many cases the original dressing was left until healing was complete. It was soon noted that this had an appreciable

effect in cutting down the healing time. The following figures represent some of the rather striking differences encountered (Table VIII).

TABLE VIII

RELATION OF NUMBER OF DRESSINGS TO HEALING TIME IN 38 LESIONS TREATED WITH SULFAFILM

Number of Dressings	Average Healing Time
5	13.8 days
3	12.1 days
2	9.3 days
1	7.6 days

In the relatively few cases treated with boric ointment the same observation was made, namely, the fewer the dressings the quicker was the healing time. We feel that the reasons are twofold: First, that removing any dressing, even where there is no obvious adherence to the burned area, undoubtedly disturbs and probably removes some of the extremely friable new epithelium. This occurs because the dressing tends to become incorporated in the lesion. Second, the factor of increased contamination which is cumulative with each dressing change may also interfere with the healing process.

Bacteriologic Findings.—As was stated, routine cultures were taken at the time of débridement and treatment. In approximately 50 per cent of the cases these cultures were positive, despite the fact as has been stated that iodine and alcohol preparation of the selected burn sites was used. In the remainder of cases cultures were negative. By far the more common contaminant was *Staphylococcus albus.* Infrequently *B. subtilis,* micrococcus tetragenes, diphtheroid bacillus and *gamma* streptococcus (indifferent) were cultured. Important, however, is the fact that no difference was encountered in the healing of lesions primarily contaminated when compared as a group with the lesions which had negative cultures originally. Subsequent infection, when encountered, appeared alike in both originally contaminated and originally sterile areas. Gross infection occurred rarely in this series, but was most common when the escharotics were applied.

Sulfonamide Sensitization.—Much has been written of late concerning development of systemic sensitivity from the local use of sulfonamides. In the present series this phenomenon occurred only once during active treatment. This was in one of the females who, as was stated, suffered a relatively deeper burn than the males, presumably due to the difference in skin thickness. One of her lesions was treated with the sulfonamide-impregnated film and on the ninth day, at which time the healing was nearly complete, she complained of itching and burning at the burn site. Examination revealed a papular rash, with vesiculation, weeping, and localized edema of the area. Not only was the burn itself involved but also the surrounding skin. This rash disappeared on treatment with bland ointments, and patch tests performed at this time on the anterior aspect of the forearm revealed apparent sensitivity to the sulfonamide-impregnated film, but none to a film of similar

base containing no sulfonamides. Passive transfer tests were uniformly negative. Retesting by the patch method both on the site of the healed burn and on the forearm was negative for further evidence of sensitization. Because of this case, however, 25 of the areas treated with the sulfonamide film were tested by reapplication of the film to the burn site at weekly intervals following healing. In six cases a rash occurred at the burn site on the first test (Fig. 9). When retested a week later, three were still positive but none was positive at the end of five weeks. In none of the six subjects was there evidence of sensitivity except at the burned areas. This pseudosensitization is mentioned only because of its academic interest, since it is unlikely that an accidental burn should occur in the same area within a short time in a single individual.

FIG. 9.—Sensitivity reaction appearing as a maculopapular rash surrounding a sulfonamide film-treated lesion one week after complete healing.

Rôle of Sulfonamide.—As we review this series of experimental burns we find several indications that the use of sulfonamides either locally or systemically may exert a definitely beneficial influence. Thus, when a sulfonamide-impregnated film was employed the burns healed in the shortest time on the whole, although positive cultures were obtained on numerous occasions. Signs of inflammation such as heat, redness and swelling, however, were quite uniformly lacking. Again, in the series in which boric ointment was used locally with sulfadiazine by mouth four out of five cultures were positive and the healing time was slightly more prolonged, but again no gross infection

or inflammation developed. When boric ointment alone was used the healing time was definitely prolonged and clinical signs of infection were in evidence.

It would seem, therefore, that the bacteriostatic effect of the sulfonamides is accompanied by shorter healing time, and that complete elimination of infection as evidenced by persistently negative cultures is not necessary for prompt epithelization of deep second degree burns.

Another point in local burn therapy which has been raised lately is whether or not a lesion should be débrided prior to the onset of definitive therapy. To answer this question, five lesions were purposely left with vesicles intact and the sulfonamide film placed over these. The contralateral areas were débrided as usual and treated with the same agent. All lesions were healed in seven days and the comparison of the new epithelium of the two sides showed little difference. In three instances the blister was still imperforate and the fluid had been *reabsorbed* while the lesion healed.

SUMMARY AND CONCLUSIONS

A controlled series of 82 second degree burns in human volunteers has been studied and the efficacy of 12 different local treatments has been evaluated.

The best results as measured by rapidity of healing, absence of symptoms and freedom from all complications were encountered in the group treated with a sulfonamide-impregnated plastic film.

The next best, and very nearly as efficacious method, was local treatment with a bland ointment combined with sulfonamides administered by mouth. However, certain qualitative differences were noted between the healing processes of lesions treated with film and those in which boric ointment was used.

The value of the use of the sulfonamides either locally or systemically was clearly demonstrated in the control of infection and the evidence of sensitivity, resulting from their local application, was minimal and of no practical significance.

The importance of restricting the frequency of dressings was confirmed, as there was a direct relationship between the rate of healing and the number of times the dressings were removed.

Under the conditions of this experimental series the lesions which were not débrided healed as well and as rapidly as those from which all nonviable tissues was carefully removed.

Our experience in this series of experimental burns gives additional evidence for the abandonment of any type of treatment with escharotic agents.

Finally, it is suggested that so-called second degree burns should be carefully described as to their depth to facilitate greater accuracy in comparing results obtained in series reported in the literature.

REFERENCES

1 Cannon, B., and Cope, O.: Annals of Surgery, 117, 85, 1943.
2 Dingwall, J. A., III: Annals of Surgery, 118, 427, 1944.
3 Gilligan, D. R., Garb, S., Wheeler, C., and Plummer, N.: J.A.M.A., 122, 1160, 1943.
4 Hoffman, R. S., and Dingwall, J. A., III: Surg., Gynec. and Obst., 79, 103, 1944.

TANNIC ACID AND THE TREATMENT OF BURNS: AN OBSEQUY*

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TWENTY YEARS AGO, on May 5, 1924, seven patients who had been burned in an illuminating gas explosion were admitted to the Henry Ford Hospital. These men became the first of a category of treated cases which, in all probability, numbers hundreds of thousands at the present time. Tannic acid was applied to their burns. All survived, and their case histories along with 18 others were included in E. C. Davidson's[1] published paper on the method which appeared in August, 1925. It is hoped that this communication from a group working in the same institution will result in the abandonment of the treatment of burns by this and related methods. This unqualified recommendation is prompted by comparatively recent clinical experience and animal experiments by us and others. Under certain circumstances, the use of tannic acid produces a severe if not a fatal lesion in the liver, and carefully controlled experiments have shown that it is moderately inhibitory to the healing of wounds.

In April, 1940, two of us[2] published a paper entitled "Problems in the Treatment of Burns: Liver Necrosis as a Lethal Factor." It was pointed out that in five consecutive autopsies, there was striking degeneration of the liver. All of the cases had been treated with tannic acid jelly. However, since the lesion had also been seen in at least one case treated by the widely used spray method,[3] the rôle of tannic acid was not immediately appreciated. Several authors called attention to the liver lesion, but did not incriminate tannic acid.[4, 5, 6, 7, 8] Notable among these were Wilson, and his associates, of Edinburgh, who were distressed with the fact that there were deaths from "burn toxemia" in children with small areas involved.

At the Clinical Congress of the American College of Surgeons at Chicago, in October, 1940, Donald B. Wells, of Hartford, took part in a panel discussion of burns, and showed photomicrographs of livers from experimental animals into which tannic acid had been injected subcutaneously. To our knowledge, this was the first public accusation of the tanning method. The article by Wells, and his associates,[9] containing reports of six clinical cases, and the animal experiments appeared in April, 1942. In March, 1942, one of us[10] led a panel discussion on burns at a War Session of the American

* Part of the work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Development and the Henry Ford Hospital.

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College of Surgeons, and called attention to the probable relationship between the liver lesion and tannic acid.

In February, 1942, a project for the study of burns at the Henry Ford Hospital was approved by the Committee on Medical Research. At the request of the Subcommittee on Surgical Infections, alternate cases were treated by two currently accepted methods, namely, the tanning and vaseline-pressure methods. Extensive studies were carried out on these patients, but only the observations regarding the liver are presented here. Four illustrative cases

FIG. 1.—Case 1: Eschar from tannic acid jelly has formed.

will be reviewed. Two of these were tanned cases and two will be called controls, *i.e.*, they were treated with the presumably inert vaseline dressing.

ILLUSTRATIVE CASE REPORTS

Case 1.—D. L., white, female, age six. She was admitted on March 17, 1942, having sustained severe burns when her clothing caught fire while she was playing with matches. She was found to have deep burns of the face, abdomen and upper extremities (Fig. 1). It was estimated that 36 per cent of the body surface was involved (Fig. 2). All blisters were removed and tannic acid jelly was applied. Plasma infusions (800 cc.) were given during the first 24 hours. A satisfactory correction of the hemoconcentration was obtained (Fig. 3). Nevertheless, the clinical course of the patient was not good. There was persistent vomiting on the second day. The vomitus was of the appearance of coffee grounds on several occasions. Bleeding from cracks in the tannic acid eschar was noted, and this observation was in agreement with the laboratory finding of a plasma prothrombin level of zero. Oxygen, whole blood transfusion and adrenal cortex were given. She became comatose, the urinary output became *nil*, and she expired on March 24. All liver function tests showed that profound hepatic

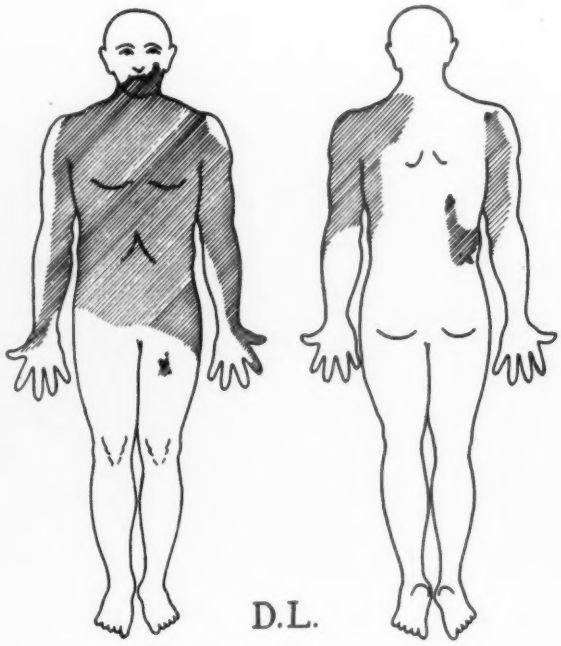

FIG. 2.—Diagram of all burned areas in Case 1.

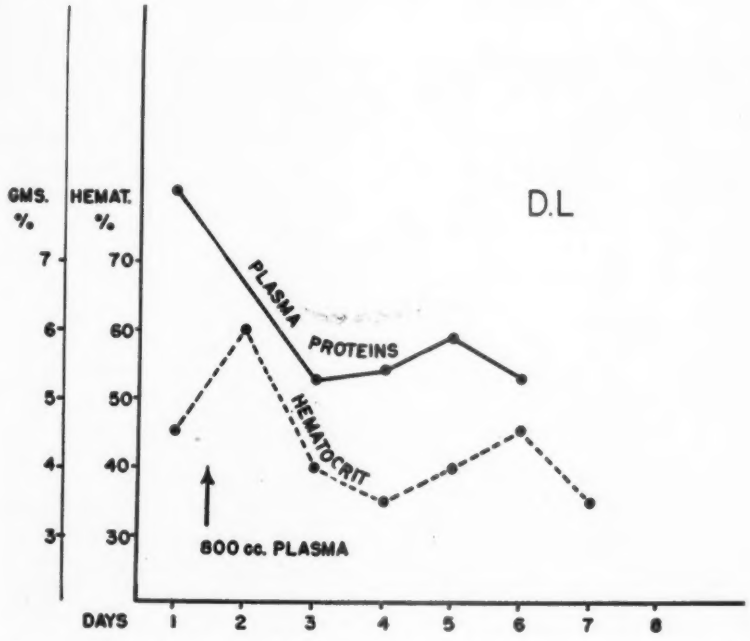

FIG. 3.—Chart of hematocrit and plasma protein values in Case 1. The correction of hemoconcentration was not accompanied by clinical improvement.

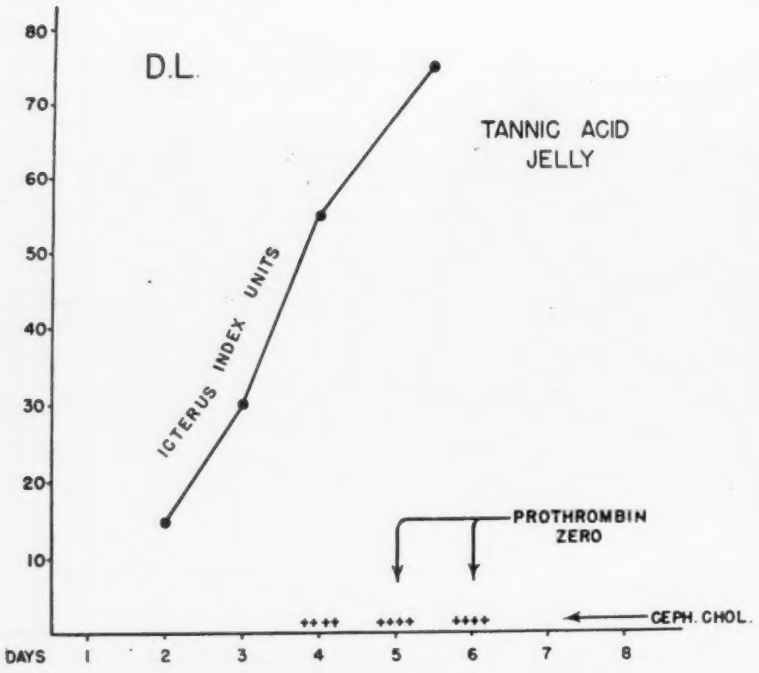

FIG. 4.—Chart of liver function studies in Case 1.

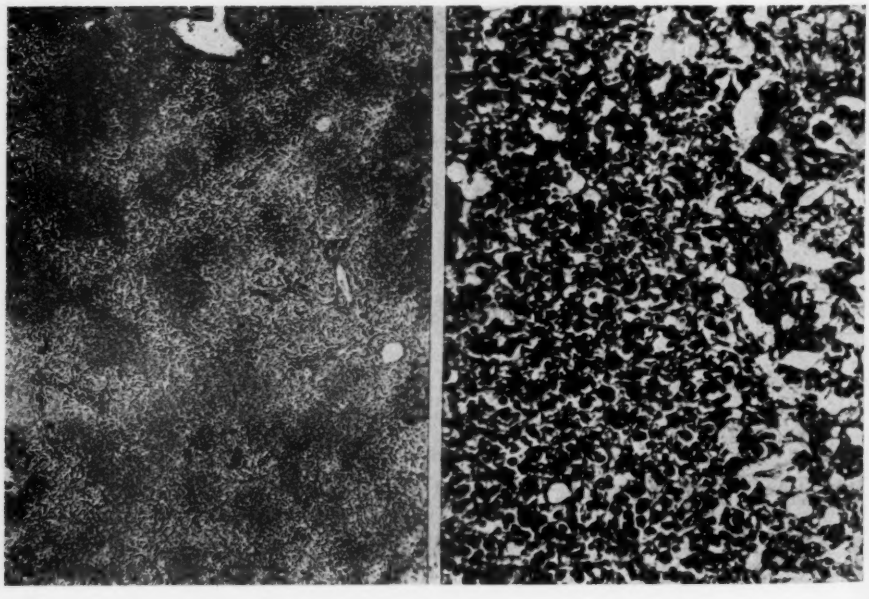

FIG. 5.—Low and high power photomicrographs of liver tissue, Case 1.

damage had occurred (Fig. 4). Autopsy was performed. The chief finding was the microscopic appearance of the liver (Fig. 5). The tissue could hardly be identified as liver tissue, so great was the necrosis.

Case 2.—M. A., white, female, age two. On May 5, 1942, her clothing caught fire and she was severely burned. She arrived at the Henry Ford Hospital three hours

FIG. 6.—Case 2: Appearance at time of first dressing (vaselined gauze, with pressure).

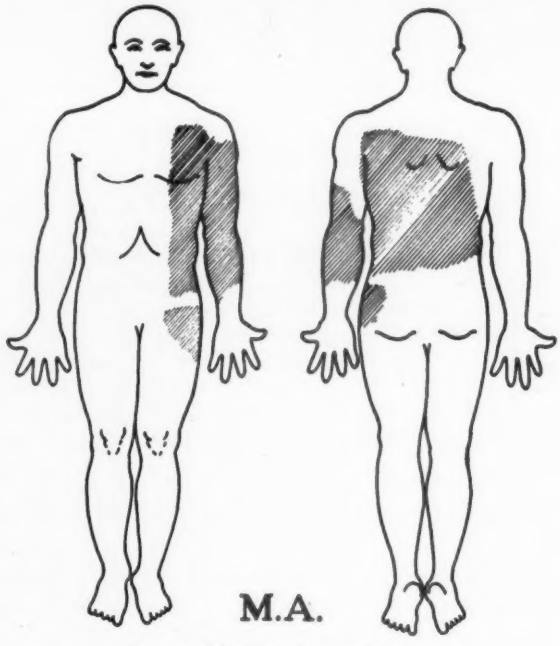

FIG. 7.—Diagram of burns in Case 2.

later. Deep burns of the back, left arm and buttock were present (Figs. 6 and 7). The blisters were removed, and cleansing was carried out with white soap and water. Fine-mesh vaselined gauze was applied under pressure with machinists' waste and

elastic bandages. These dressings were not disturbed for two weeks. Although there was some fever, at no time did the girl look dangerously ill. Liver function tests showed essentially normal values (Fig. 8). Three skin grafting operations were necessary to cover the areas of third degree burn, the first procedure being on May 26. She was discharged on June 21 in excellent condition.

Case 3.—E. S., white, male, age 16. On April 21, 1942, he was working in a gasoline station and his oil-soaked trousers became ignited. There were second degree burns of the lower extremities, estimated as 22 per cent of the body surface (Fig. 9). Blisters were removed and tannic acid jelly was applied within an hour of the injury. He received 900 cc. of plasma. Nausea, vomiting and extreme lethargy developed on the third day and persisted for a week. Clinical jaundice appeared on the third day.

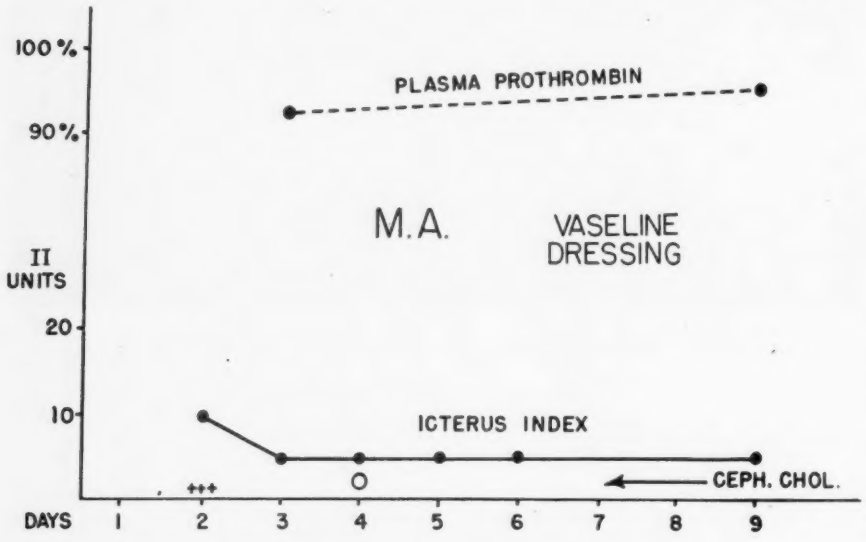

FIG. 8.—Chart of liver function studies in Case 2.

Liver function tests showed marked disturbance of hepatic function (Fig. 10). Infection developed beneath the eschars on both legs. Healing was complete on May 29.

Case 4.—C. L., white, female, age 28. She was burned in a gas explosion on August 18, 1942, and was admitted to the hospital an hour later, with burns of 31 per cent of the body surface (Fig. 11). She was treated with vaselined gauze and pressure dressings. She received 2400 cc. of plasma. The dressings were changed on the eleventh day, and most of the burned areas were healed. The liver function studies did not deviate from the normal except that the cephalin-cholesterol test was slightly positive on the third and fifth days (Fig. 12).

As far as we know, there are no substantiated cases of liver damage of the grade described in Cases 1 and 3 in patients who have not had their burns treated with tannic acid. Others[11] have gone over their pathologic material and have found that the hepatic lesion was present only in the tanned cases. The lesion has been reproduced in experimental animals by a number of investigators.[12, 13, 14, 15]

In addition to the toxic effect just considered, there is an unfavorable local effect of the tanning method. Wound healing is considerably delayed

and border-line second degree burns may be converted to third degree. In 1936, Taylor[16] issued a timely word of caution in an article entitled "The Misuse of Tannic Acid." He pointed out that the "fixing" of tissues, as with tannic acid, meant cell death, and that there was danger of live cells being thus "fixed."

The Padgett dermatome has made possible a convincing type of wound healing experiment. It is possible to obtain two wounds of similar size and depth, one serving as the treated and the other as the control wound. Experiments of this kind, using tannic acid, have been carried out by Cannon and Cope,[17] in Boston, and Hirshfeld, Piling and Maun, in Detroit.[18] Tanning has invariably produced a delay in the healing of these dermatome-donor sites. The latter investigators took biopsies of tanned tissue at various intervals and demonstrated that the depth of the injury can be increased considerably by the use of escharotics.

Brush, Lam and Ponka[19] found that both the 5 per cent aqueous solution of tannic acid and the jelly caused delay in the healing of experimental cutaneous wounds in the guinea-pig (Fig. 13).

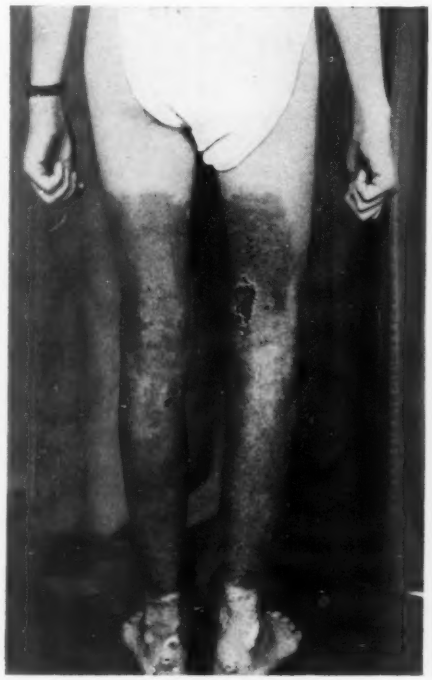

FIG. 9.—Case 3: Burned areas. Healing is almost complete. Tannic acid.

If tannic acid is toxic to the liver and does local damage, why was it used for 20 years, and why was it adopted so enthusiastically almost all over the world? What about the much publicized mortality rate reductions? We fear that the largest factor was "wishful thinking." The management of a badly burned patient was (and still is) such an onerous task that any method with possibilities would have been received with open arms. Scientific evaluation of a burn remedy is notoriously difficult and unreliable. It has taken 20 years to evaluate tannic acid. A review of the early articles on this method of treatment shows that many of the reported series were remarkably small. Many times, the mortality was high, but various alibis were given. One paper[20] reported that the death rate had been cut in half by the new treatment, but it is noted that the primary mortality rate was unreasonably high (40 per cent). As a matter of fact, the mortality rate at the Henry Ford Hospital was not improved with the adoption of tanning, a fact which was indicated by statistics published in 1935[21] and 1940.[2] These figures and the most recent ones may be seen in Table I.

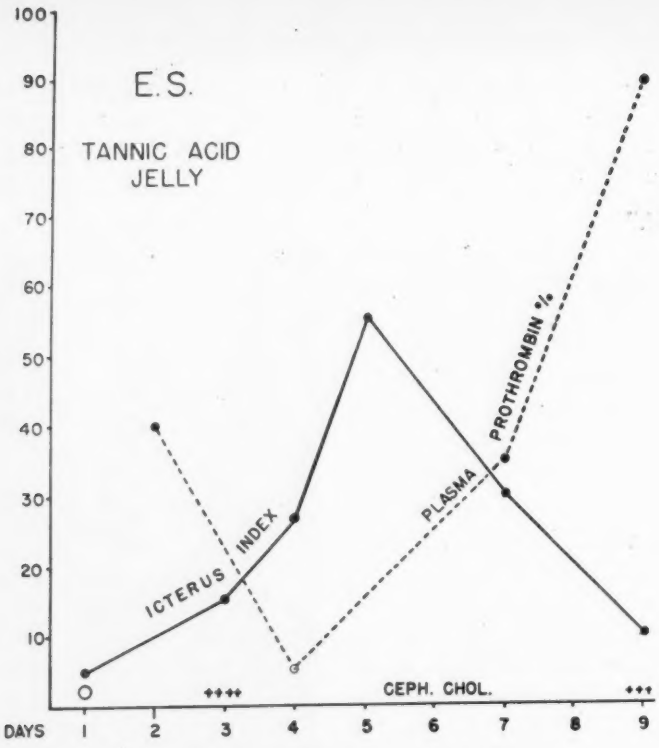

FIG. 10.—Chart of liver function studies in Case 3.

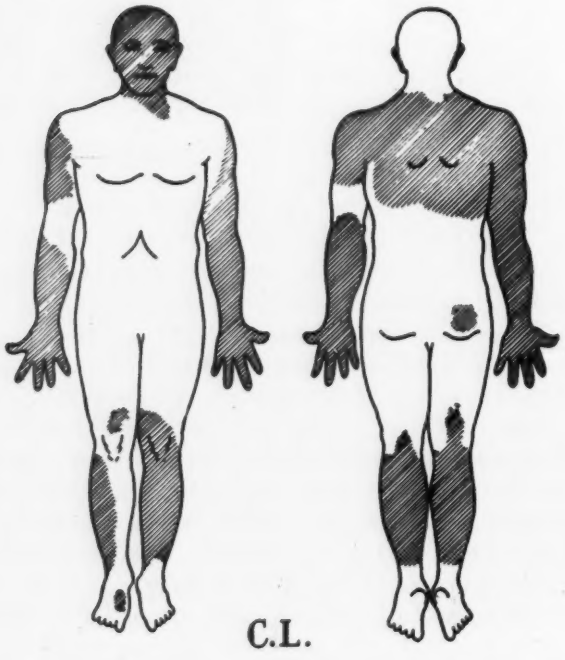

FIG. 11.—Case 4: Diagram of burns. Vaseline dressings were used.

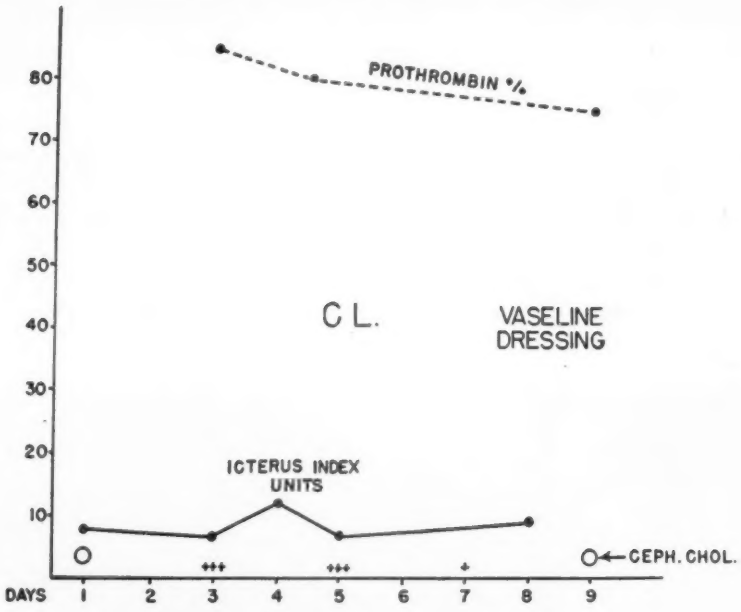

FIG. 12.—Chart of liver function studies in Case 4.

FIG. 13.—Wound healing experiment showing inhibiting effect of tannic acid jelly. Both wounds were the same size ten days before. Control wound (arrow) is healed.

TABLE I

BURN MORTALITY RATE AT HENRY FORD HOSPITAL

Date	Method	Cases	Deaths	Mortality Rate
1916–24	Various	118	11	9.3%
1925–36	Tannic acid	358	42	11.7%
1936–40	Tannic acid jelly	125	22	17.6%
1942–44	Vaseline	80	2	2.5%

It is probable that in many hospitals there was an actual decrease in the mortality rate during the "tannic acid era." After Davidson's paper, there was infinitely greater interest in burns. All aspects of treatment became better. In the more recent years, severe cases were given large amounts of

FIG. 14

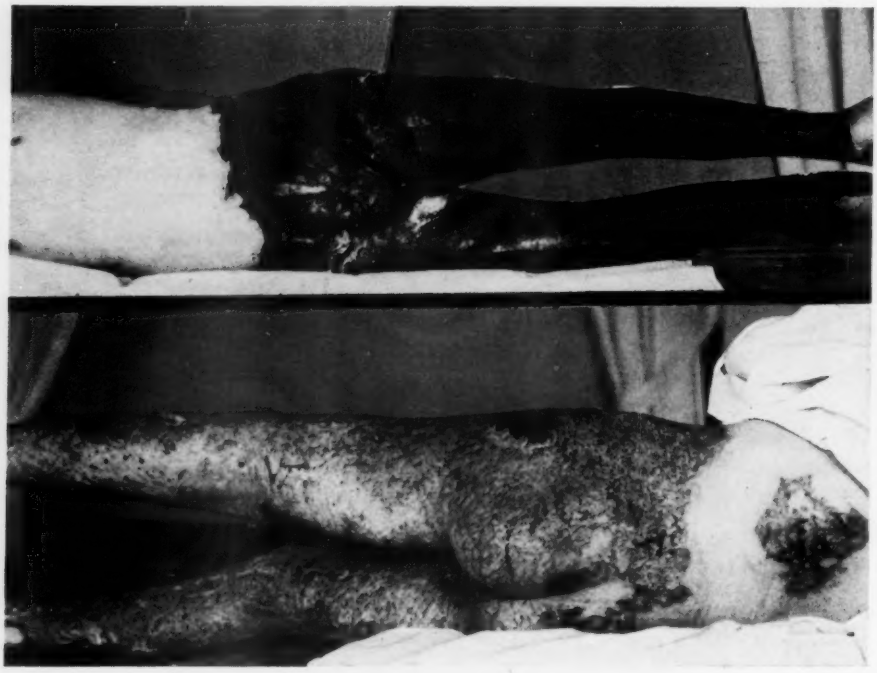

FIG. 15

FIG. 14.—Case 5: Showing well formed tannic acid eschar.
FIG. 15.—Case 5: Four weeks after injury. Subcutaneous fat is visible everywhere on lower extremities. The depth of tissue necrosis prevented tannic acid absorption.

plasma in addition to their tanning treatment. It is obviously improper to assume that the recovery of such a case was due to the local treatment.

Some explanations are at hand regarding the inconsistency of the appearance of the specific liver lesion. The method of application may have increased the rate and amount of absorption. It is undoubtedly significant that the cases reported by Wells were treated in a tub bath, and most of our own cases were treated with a jelly, which was relatively slow to dry. Many severely burned patients did not absorb much tannic acid on account of the

extreme depth of their burns. A second degree burn presents the best absorbing surface. The following case is one in which there was probably little or no absorption due to the uniformly great depth of the burn:

Case 5.—B. S., white, male, age 21. Admitted on February 11, 1941, after his oil-soaked clothes caught fire. He had a third degree burn corresponding to the area covered by his trousers. A good eschar was obtained with tannic acid jelly (Fig. 14). He was given 2500 cc. of plasma. At no time did he show signs of shock or any symptoms of hepatic insufficiency. The icterus index during the first month was not above 10. Tissue injury was extreme, however, as can be seen from a view taken after four weeks, showing all of the eschar removed, and no epithelium visible from the heels to the waistline (Fig. 15). This patient expired on the fifty-fifth day, of inanition and sepsis. He became refractory to transfusions of any type, and was not benefited by the heroic gesture of homografting. However, his death was not related to early burn shock or toxemia.

SUMMARY

Liver necrosis has been reported in a considerable number of burned patients treated with tannic acid. Nonfatal cases frequently show marked disturbance of liver function in the acute phase of the burn. The liver lesion is easily reproduced experimentally. Wound healing experiments on animals and on human donor sites indicate that tannic acid retards healing considerably.

In writing this "obsequy" for the tannic acid treatment of burns, it is far from our desire to write off the work of the late E. C. Davidson. He was an indefatigable worker and a keen observer. Had he lived, he might have recognized the shortcomings of his method before the others we have mentioned. It is certain that we would be further along on the burn problem if we had had his help beyond 1933.

REFERENCES

1 Davidson, E. C.: Tannic Acid in the Treatment of Burns. Surg. Gynec. & Obst., **41**, 202, August, 1925.

2 McClure, Roy D., and Lam, C. R.: Problems in the Treatment of Burns: Liver Necrosis as a Lethal Factor. Southern Surg., **9**, 223, April, 1940.

3 McClure, Roy D.: The Treatment of the Patient with Severe Burns. J. A. M. A., **113**, 1808, November, 1939.

4 Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds under Modern Methods of Treatment. Brit. J. Surg., **25**, 826, April, 1938.

5 Belt, T. H.: Liver Necrosis Following Burns Simulating the Lesions of Yellow Fever. J. Path. and Bact., **48**, 493, May, 1939.

6 Boyce, F. F.: The Rôle of the Liver in Surgery. Springfield, Ill., and Baltimore. Chas. C. Thomas, 1941.

7 Lam, C. R.: The Chemical Pathology of Burns. Surg., Gynec. & Obst., **72**, 390, April, 1941.

8 Duffin, J. D.: Liver Necrosis Following Burns. Canad. Med. Ass. J., **47**, 138, August, 1942.

9 Wells, D. B., Humphrey, H. D., and Coll, J. J.: The Relation of Tannic Acid to the Liver Necrosis Occurring in Burns. New England J. Med., **26**, 629, April, 1942.

10 Lam, C. R., and Harkins, H. N.: Treatment of Burns, Bull. Am. Coll. Surg., **27**, 109, April, 1942.

[11] Erb, I. H., Morgan, E. M., and Farmer, A. W.: The Pathology of Burns. ANNALS OF SURGERY, **117**, 234, February, 1943.

[12] Hartman, F. W., and Romence, H. L.: Liver Necrosis in Burns. ANNALS OF SURGERY, **118**, 402, September, 1943.

[13] Forbes, J. C., and Evans, E. I.: Tannic Acid and Liver Necrosis. Surg. Gynec. & Obst., **76**, 612, May, 1943.

[14] Barnes, J. M., and Rossiter, R. J.: Toxicity of Tannic Acid. Lancet, **2**, 218, August, 1943.

[15] Clark, E. J., and Rossiter, R. J.: Liver Function in Rabbits after Injection of Tannic Acid. Lancet, **2**, 222, August, 1943.

[16] Taylor, Frederic: The Misuse of Tannic Acid. J. A. M. A., **106**, 1144, April, 1936.

[17] Cannon, Bradford, and Cope, Oliver: Rate of Epithelial Regeneration: A Clinical Method of Measurement and the Effect of Various Agents Recommended for the Treatment of Burns. ANNALS OF SURGERY, **117**, 85, January, 1943.

[18] Hirshfeld, J. W., Pilling, M. A., and Maun, M. E.: A Comparison of the Effects of Tanning Agents and of Vaselined Gauze on Fresh Wounds of Man. Surg. Gynec. & Obst., **76**, 556, May, 1943.

[19] Brush, B. E., Lam, C. R., and Ponka, J. L.: Wound Healing Studies on Several Substances Recommended for the Treatment of Burns. To be published.

[20] Bancroft, F. W., and Rogers, C. S.: Late Treatment of Burns. Arch. Surg., **16**, 979, May, 1928.

[21] McClure, Roy D., and Allen, C. I.: Davidson Tannic Acid Treatment of Burns: Ten-Year Results. Am. J. Surg., (N.S.), **28**, 370, May, 1935.

DISCUSSION.—DR. JONATHAN E. RHOADS, Philadelphia: We are grateful to Doctors McClure, Lam and Romence for their paper, because it will be helpful to surgeons everywhere to know that the tannic acid method has been abandoned by the institution from which it was introduced.

One of the perplexing things about the history of the tannic acid method is the tremendous clinical experience which attested its value in reducing burn mortality. Nearly every report except that which Doctor McClure made several years ago, mentioned a reduction in mortality of approximately 50 per cent. It has been suggested that the improved mortality was due to other changes in treatment, but it seems doubtful if such a large number of good clinical observers would have overlooked this fact had it been true.

Even if it should be true that the reduction in mortality was brought about by other factors, it is difficult to believe that the tannic acid method, as generally used, actually caused the death of many patients who were not going to die anyway.

Those who died with a picture of toxemia generally showed marked changes in liver function, and during the period when tannic acid was widely used the changes in liver function and the histologic changes in the liver of those patients who died were regarded by many people as the cardinal signs of toxemia.

At the Pennsylvania Hospital since the tannic acid method has been given up, we have observed that toxemic deaths still occur. In fact, since the advent of better methods of treating burn shock, a larger proportion of deaths following burns appears to be due to toxemia.

Recent studies, carried out under contract with the Office of Scientific Research and Development, indicate that mild changes in liver function still occur in patients treated with vaselined gauze and pressure dressings.

In this series of patients you will notice that the cases have been classified according to the rise in the van den Bergh test. A number of other liver function tests were carried out, and of the group the van den Bergh seemed to be most representative of the changes observed.

Twenty-nine per cent of the patients treated with tannic acid had an elevation of

the serum bilirubin of two milligrams, or more, and all of the extremely high elevations, such as one of 11, one of 13 and one of 16 milligrams per cent, occurred in that group.

Patients treated with other tanning methods, mainly silver nitrate or silver nitrate and methyl rosanilin, had a rise in the bilirubin of over two milligrams in 17 per cent, and those treated by nontanning methods in only seven per cent.

We agree that the evidence against the use of tannic acid is so definite that it should be abandoned. However, it is difficult to escape the conclusion that the method was a useful one during the years following its introduction; that it probably caused very few liver deaths in patients who would not have died anyhow; that it was perhaps the first type of dressing that was not changed during the first ten days; and that it did tend to prevent infection during the early stages when the patient was in his greatest danger from shock and toxemia.

Undoubtedly, one of the reasons which has facilitated the revival of methods similar to methods which tannic acid displaced, is the possibility of controlling invasive infection by the use of sulfonamides.

DR. ALLEN O. WHIPPLE, New York: Of the many problems studied by the Subcommittee on Burns of the National Research Council none has been more difficult than the treatment of the extensive third-degree burn. As a result of the newer measures for combating shock and infection, many of these severe burns that formerly died in the first three to five days survive to become problems in chronic infection, hypoproteinemia and nitrogen imbalance, anemia, weight loss and nutrition deficiencies. Removal of the slough and skin grafting of the remaining granulating area of these patients, shorten their hospital stay and minimize their scarring and contractures than any other therapeutic measure.

The hastening of the sequestration and removal of the slough have been under investigation during the past two years by Beard, of Duke University, using papain and salicylic acid, and by Howes, of Columbia University, using hydrochloric acid and pepsin, and many other acids and enzymes. But by these methods, although the slough was liquefied and disappeared quickly, the remaining surface was not a suitable one for the taking of skin grafts.

Doctors Harvey and Conner have made a real and significant contribution in their use of pyruvic as a means of removing whole-thickness slough, leaving a suitable granulating surface for immediate or prompt skin grafting. If the clinical results will be in any way comparable to the experimental burns we have seen in their laboratory a great step forward will be taken in the treatment of whole-thickness burns.

We have found a great difference, however, in the use of pyruvic acid on small areas as compared with extensive areas of slough. In the former it is possible to keep the acid active in a starch base, but in an extensive slough, with considerable exudation and with considerable variation in the thickness of the slough, the maintenance of the optimum p_H of 1.9 is difficult and the slough does not separate evenly.

However, in the few patients upon whom we have used this preparation, it is evident that the acid does not damage normal skin; it does not convert second-degree areas into third-degree; it demarcates third-degree areas early; it is painless; and it undoubtedly causes an early separation of slough, leaving a granulating base suitable for early skin grafting.

There are several problems that will have to be studied carefully before the method can be generally recommended. One is the question of what the limit of the area is on which the pyruvic acid is applied before an acidosis is produced. Secondly, is there a danger in removing too extensive a slough, leaving a granulating surface that cannot be promptly skin-grafted without removing an amount of normal skin beyond the donor area limit in amounts that would cause severe shock? Stamp-grafting areas from which slough has been removed at intervals would be necessary in extensively burned patients.

DR. CHARLES C. LUND, Boston: These four papers are very difficult to discuss because they bring up, in one way or another, most of the important problems of burns, and in five minutes I can only select one or two things to consider.

Doctor Andrus' experimental burns are very ingenious, a very useful method, and I think Doctor Dingwall's results are very important. To me the most important table was almost the last table that he presented, that is, that the less often you dress a burn, the faster it heals.

I have felt that so strongly that recently, at a meeting of doctors under the auspices of an insurance company, with some of the insurance company's officers present, I suggested that maybe the insurance company should take a leaf from the New Deal and find out how many dressings the fussiest doctor would be apt to do for a given burn, and then pay the doctor a flat rate for not doing those dressings.

The difference between boric ointment and the sulfa film was certainly significant and interesting. I have become such a therapeutic nihilist on the subject of chemical applications to the surface of burns, that, as some people know, we have given up any application now except dry gauze, counting on rest, pressure with or without plaster, as creating as good conditions as we know of for the healing of a burn, and allowing those dressings to remain up to three and even four weeks.

The conditions here, with ambulatory patients, certainly do not give the conditions of rest that you get in a suitable Allen-Koch type of pressure dressing.

I was a little surprised that there was as much evidence of infection under the boric ointment treatment, either with or without sulfa drugs, as there was in this series, and I can explain it only on the basis that if these men had been in bed during the treatment, there might have been somewhat less infection.

However, the conclusions of this paper and the data are quite important, and they are another expression of the fact that we must avoid employing any treatment that delays the healing of a burn. We cannot actually stimulate the healing of a burn. The healing of a burn is done by nature; if we can create the right conditions, nature can heal it very rapidly.

Just a word about Doctor Moyer's paper: In the first place, I want to ask him a question: How much hemoglobinemia was seen in these dogs with their extensive deep burns? From the experiments in much smaller burns of dogs and calves that C. K. Drinker, of Boston, has carried on, I would have expected there would be a great amount of blood destruction from the thermal injury of the blood in and under the skin in these dogs.

This paper has given me a great deal to think about, and I believe it is as important or more important than any paper I know of on the chemical aspects of burns in the last two or three years.

We are finding, by chemical tests on human patients, that there are very significant differences in the chemical blood changes associated with deep extensive burns from those changes of the same items in the widespread second-degree burns, and the problem of treating the extensive third-degree burns is certainly, according to our data in our hands, a much more complicated one than just trying to keep the hematocrit at a reasonable level by pouring in plasma.

We have not anything published on it yet, but we ourselves are getting very suspicious of possible harm from the citrate in the ordinary plasma when we are using three or four liters of plasma.

We are also very doubtful about lactate, as Doctor Taylor of our group will present shortly. The blood lactic acid goes up as much as ten times in some burns without the administration of any lactate. The sodium bicarbonate in the blood, if the burn is very severe, may go down, and it may go down to a significant extent.

Therefore, it is quite logical that if you are to treat to prevent or treat acidosis,

you had better do it by bicarbonate rather than by lactate. We cannot put that out as final, but it is one of the things we are working on.

I was delighted at Doctor Connor's and Doctor Harvey's method of removing slough, and I am glad to hear that at least it is not dangerous to apply to humans.

It looks to me like the kind of thing that many of us would like to use in cases very shortly.

DR. ALFRED BLALOCK, Baltimore, Md.: I have never been an advocate of the tannic acid method for treating burns, but I doubt if the method should be completely abandoned. It might be the expedient method when numerous burns have to be treated on a ship. I would certainly doubt the wisdom of placing on large pressure dressings under such circumstances if there is a possibility that the ship will have to be abandoned.

My purpose, however, is to discuss the paper by Doctor Moyer, and his associates. I agree with Doctor Lund that this is an excellent study. A great deal of attention has been focused recently on the treatment of burns and other injuries by the use of salt solution. Much of this interest is due to the work of Rosenthal, of the Public Health Service, on the treatment of burns in rats and in mice. He finds that all sodium salts are equally effective and that the administration of salt solution by mouth or by vein is as effective as the intravenous use of blood serum or blood plasma. One criticism which has been levelled at these experiments is that the treatment is carried out almost immediately after the infliction of the burn. A second criticism is that tremendous quantities of fluid equal to 8 to 15 per cent of the body weight are given. Even if his observations apply in man, a real difficulty would be encountered by the armed forces under many circumstances in having available such large quantities of fluid.

Doctor Prinzmetal has also carried out similar experiments on rats and mice and he finds, also, that isotonic saline is as effective as plasma.

Doctor Haist, of Canada, on the other hand, has been studying a somewhat similar type of injury, namely, tourniquet shock. Hemoconcentration occurs under these circumstances just as it does in burns. He waits several hours in these studies before carrying out therapy and finds that salt solution is far inferior to plasma therapy. Dr. C. N. H. Long, of Yale, has produced shock by the slow withdrawal of blood, and, here, it is found that plasma is far superior to salt solution.

Doctor Moyer, and his associates, as you have heard, have come to the conclusion that the administration of defibrinated blood by vein and of salt solution by other routes constitutes the ideal treatment for experimental burns in dogs. The method which they have used in causing burns consists of immersion for 30 seconds. This type of "cooking burn" is not encountered frequently in man.

The emphasis which some of these investigators have placed on the giving of fluids by routes other than the intravenous one raises the question as to whether fluids will be retained and absorbed when given by mouth and whether they will be absorbed when given subcutaneously or by rectum.

Patients in shock are very apt to vomit when given large quantities of fluid by mouth. The question arises as to whether the vomiting is due to impaired circulation or whether it is due to morphine which may be given to control pain. It is stated in a recent note from Major Beecher in North Africa that the vomiting is frequently due to the morphine. I am inclined to think, however, that many patients in shock will vomit even though no morphine is given. Certainly it is true that patients in severe shock absorb fluid from the tissue spaces very poorly. It is agreed that fluids should be given by mouth if they are retained.

Doctor Fox has reported good results in the treatment of burns in man by the use of sodium lactate by mouth. The experience of Dr. E. I. Evans, of Richmond, in this regard has not been so encouraging. Doctor Evans is here and I hope that he will comment upon this point.

It would seem to be a fundamental principle in fluid replacement that one should re-

place the loss as nearly as possible by fluid of the same composition. It is an incontrovertible fact that large quantities of plasma containing protein are lost at or near the site of severe burns. It would seem that the burden of proof is on the person who says that the treatment of burns should not include the administration of blood plasma. If fluids containing sodium salts are retained and absorbed when given by mouth, it would appear that this makes for an additional important therapeutic aid. I am confident, however, that the use of such sodium salts to the exclusion of plasma will result in a great deal of harm. We should continue to use plasma in the treatment of burns unless it is shown by studies on man that other methods are equally effective.

Dr. Everett Evans (Dept. of Surgery, Medical College of Virginia, Richmond, Va.): At Doctor Blalock's invitation I would like to discuss these papers very briefly, because I think we have had a great amount of clinical experience with severe burns.

Our service has had now close to 200 hospitalized burns. First, we agree with almost everything that Doctor McClure has said about tannic acid. Fortunately for us we stopped the use of tannic acid when we took over the treatment of burns as a research project. In the present series, the only patient treated with tannic acid (by error), a child, died on the seventh day with a history that reads almost exactly as the one presented by Doctor McClure.

We would take exception to one statement in the abstract, that is, "that there need be no concern about the liver in a burned patient if tannic acid is not used."

We have now four extensive burns (not treated by tannic acid) that have come to autopsy. By "extensive" I mean 60 to 85 per cent of the body surface burned; each of these has shown a moderate to very severe liver damage on histologic section. It may be that we are dealing here with liver damage in patients in acute starvation. They lived for from five to seven days.

Our experience with sodium lactate, following Doctor Fox's contribution, has been very disappointing. There were three deaths, consecutively, in patients treated with sodium lactate. It did not control the shock; unfortunately, in two cases we got in only a very small amount of lactate because the children died very shortly after the therapy was started.

In the one case treated very heroically with sodium lactate, blood volume studies (and I may say incidently we do blood volume studies by the dye technic on most patients) indicated that sodium lactate had no effect whatsoever in increasing the plasma volume of this severely burned patient. In fact, it stayed about 17 cc. per kilogram, or 30 per cent of normal, until plasma was given.

I think Doctor Whipple would be interested in our recent experience with the rapid removal of a third-degree burn slough which, I am sorry to say again, unfortunately ended in death. At the suggestion of the Burn Committee we had the Duke University group come and try their solution on a burned child 8 years of age, with a 60 per cent surface burn, third-degree. It was elected to treat only one-half of the burned surface at one time. I must say these men that Doctor Beard sent up were extremely careful in everything they did.

We did blood volume studies, gave transfusions and large amounts of fluid. The child, unfortunately, died about eight hours after treatment was started, in what seemed to me to be severe shock.

So it seems to us who have had some experience with very widespread third-degree burns, that it is probably far better to remove slough slowly in an extensive burn, better to pay the price of having some scarring, than to lose a life with the rapid removal of third-degree slough.

Dr. Roy D. McClure (closing): We did not bury this treatment too deeply. I was hoping Colonel Robert Harris might discuss this subject. I know there are many advocates still of the tannic acid treatment, and a lot of people do believe in a resurrection. We do not at the moment.

We have searched for liver sections from patients dying as a result of burns, which might show a central necrosis similar to that produced by tannic acid. This search has been without success. One of our men has offered a prize for such sections, and I am sure Doctor Lam will be especially anxious to see Doctor Evans' cases.

One thing that has held up tremendously the advance in the study of the cause of death after severe burns, is the fact that these cases are always cases for the coroner. Too often the coroners have reviewed the corpse and refused an autopsy, with the statement that: "Anyone can see that *that* patient died from a burn!"

DR. J. WALTER VAUGHAN, Richmond, Va.: It does seem unnecessary at the moment to show slides showing the extent of an injury, but I should like to show them anyway, if I may.

(Slide No. 1) This shows an incision of the subcutaneous tissue and the marked hemorrhage that occurs adjacent to the skin.

(Slide No. 2) This slide shows a kidney which I shall not comment upon at the moment, but you will see the small bowel adjacent to the kidney, which does show a degree of injury.

(Slide No. 3) This is an interesting slide showing an animal that has been treated with serum and saline, using a knife handle as the index of the degree of edema, and a bit of normal skin and subcutaneous tissue as the white tuft immediately above the injured area, with the blood less than half the amount if edema of this nature occurs.

(Slide No. 4) This slide shows a heart with marked subepicardial hemorrhages along the anterior descending coronary artery.

(Slide No. 5) This is an interesting slide showing a lung and an interesting reaction along the proud pleura, with marked hemorrhages along the intercostal vessels.

DR. CARL A. MOYER (closing): In answer to Doctor Lund's question, the slide that you saw showed dogs that were treated with saline and serum. That degree of hemorrhage is almost invariably present when this form of therapy is employed. The amount of hemorrhage present in animals treated with blood I. V. and water by mouth was about one-third of that seen in animals treated with serum. The hemoglobeinemia amounted to as much as 1.6 Gm. per 100 cc. in the period immediately following the injury; it usually decreased sharply within one hour. The largest amount of hemoglobin collected in the urine in 24 hours was 13.0 Gm. After the first day there was no appreciable hemoglobinuria.

As I said before, the tendency to generalized bleeding is present when serum and saline, and red blood cells and saline, are injected intravenously after the scald. If blood is given with salt, the generalized bleeding does not occur.

In the animals that were successfully treated (blood I. V. and saline bicarbonate orally) the treatment was begun with the administration of the salt solution one and one-half hours after the injury. The addition of blood was withheld for three hours. At that time a majority of the animals showed distinct signs of shock. It was interesting to notice that the movement of the salt solution out of the stomach within the first hour and a half was usually very small, and many of the animals vomited before the blood was given intravenously.

After the blood was given intravenously the rate of the stomach emptying approached 30 cc. per kilo per hour, which is within the normal range of movement of fluid out of the stomach in normal dogs.

We have, likewise, seen this phenomena in man, that is, in the absence of adequate blood replacement vomiting is common, and fluids given orally are not retained. After adequate replacement of the blood has taken place, they do not have as much trouble keeping the fluids down as they had before.

The composition of the salt solution is also pertinent to vomiting. The observations

of Underhill suggest it. He noted that should vomiting occur in burned men who had been given a large amount of isotonic saline that the administration of 5 to 10 Gm. of sodium bicarbonate would frequently stop it.

We hold no brief that plasma is not of value. However, the only thing that we have to say is that we are incapable of handling serum safely in dogs injured as severely as these and that serum (or plasma) is not as innocuous a substance as we have been led to believe.

There is no question whatever in my mind that should we reduce the degree of thermal trauma we could effect recovery with the combined use of serum and sodium chloride, sodium bicarbonate solution, as well as with blood and interstitial salt solutions, and if we would reduce the injury more we could effect recovery with salt solutions alone.

Dr. Frederick A. Coller (closing): We have not had the opportunity to try this on human beings. It is our misfortune, and perhaps the fortune of the patients, that in our clinic we see very few burns. However, we do feel that the principles which have been discussed this morning, which have been developed in the experimental animal, have application to other clinical syndromes as well as those of burns.

I mention it now in the hope that some of our friends who may see these lesions may have an opportunity to try out these things that Doctor Moyer has mentioned. We feel that crushing injuries at times are quite analogous to burns and may be managed in the same way. We have had two cases of acute venous occlusion resulting in hypotensive states, with loss of four liters of fluid of some kind to the site of the lesion by our calculations, which presented this same problem, and which were treated along these lines. We feel that some of the gas gangrene infections may also give use to abnormal states that may well be treated along this line. I exclude, of course, the bacterial aspect of it.

I simply mention these other clinical pictures, in the hope that some of you who may see them will be good enough, within the next year, to try some of this therapy.

Dr. Samuel Harvey (closing): In the presentation we did not go into the clinical application of pyruvic acid because the experimental work is still going ahead, and we have not adopted any standard application of it in the clinic.

It is quite certain the pyruvic acid, like succinic acid, has very little likelihood of being toxic from any possible absorption from burns. It is probably destroyed rapidly in the body because it is concerned in the intermediary carbohydrate metabolism normally.

The question of removal of third-degree slough over a large area, and the systemic effect of so doing, is certainly a pertinent one, and it is not desirable that this method should be applied except in relatively small third-degree areas until one has gained adequate experience.

Inasmuch, as the clinical application of it has been opened up in this discussion, I think I should ask Doctor Connor to present briefly some material that we have.

However, I should like to say that our reason for not presenting clinical material was that we are not prepared, nor do we desire, to have this method applied until we, as well as certain other selected groups, have had sufficient experience so that all the details of the application of it can be given with the proper safeguards.

Dr. Gervase J. Connor (closing): For emphasis I should like to repeat that this method was standardized in animals, with a view to determining whether or not with it could be satisfied the three objectives we had set up, namely: (1) The rapid removal of the slough; (2) without significant injury to living tissue (*i.e.*, the conversion of deep second- into third-degree burns); and (3) the development of a base which would immediately accept a graft.

Obviously, this question is first in importance. The experimental results have shown that these objectives can be satisfied in burns in animals.

This cannot be taken necessarily to mean that in the treatment, since there may well be a different optimum with respect to the manner of application of the method under these conditions. The results shown in the following slides indicate that the problem of removing the slough in burns in patients should be satisfactorily soluble by this method, although further study is necessary to perfect its use under these conditions.

(Slide No. 1) This is a patient who was admitted one week after a fire burn of the leg. He had been treated at home, the local treatment including cod-liver oil and various ointments, and came to the hospital only when he had developed a local infection. The wound was treated with a *generous* application of pyruvic acid paste at a p_H of 1.9. It is pertinent here to emphasize that the paste must be maintained in place, for otherwise one can scarcely expect the slough to separate rapidly.

(Slide No. 2) In this patient the slough separated completely within six days after admission in spite of the fact that for the first three days the pyruvic acid paste was not reapplied. The base of the wound was then acceptable for immediate grafting.

(Slide No. 3) This slide shows the undamaged strip of unburned skin on the back of the same leg, which area of skin was included under the dressing.

The wound was subsequently grafted after further exposure to the same pyruvic acid paste, there being no evidence of injury to the base of the wound after this additional treatment.

THE SURGICAL TREATMENT OF CARCINOMA OF THE BODY OF THE PANCREAS*

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RESECTIONS OF CARCINOMA of the body of the pancreas have been reported on rare occasions since the first solid tumor of this organ was excised in 1882 by Trendelenberg. Up to 1930, Oberling and Guerin[1] were able to collect only 11 instances of successful resections of malignant neoplasms of the body. These included four "epitheliomas" and seven sarcomas. The literature since 1930 contains but few reports of such cases. In Gordon-Taylor's[2] patient, a male, age 54, a large epithelial tumor arising in the midportion of the body was excised in 1927 but not reported until 1934. In 1938, Doberer[3] reported two instances of resection of carcinoma of the body of the pancreas; in one, the tumor arose from the superior border and was about "the size of a prune," in the other the neoplasm was quite large, involved the distal seven centimeters of body and tail, and also necessitated splenectomy. The first patient was well two and one-half years later, the second died on the fifth postoperative day. In the patient cited by Milhet, Dormay and Feyel[4] in 1940 a large carcinoma of the body was resected. There was relief from pain but finally cachexia and death two months later. In the series of six patients with pancreatic cancer reported by Harvey and Oughterson[5] in 1942, their "Case i" presented a carcinoma of the body that was resected by subtotal pancreatectomy; there was survival for five months, death being due presumably to metastasis. In 1943, Rockey[6] reported an instance of subtotal pancreatectomy for carcinoma extensively invading the organ; the patient died 15 days later of bile peritonitis.

The purpose of this communication is to record a small personal series of patients in whom attempts were made to deal with carcinoma of the body of the pancreas. There were six resections of the body, including the spleen, and two total pancreatectomies, including total duodenectomy and splenectomy.

The technic for resection of the body of the pancreas has been evolved principally as a result of experience in recent years in excision of pancreatic tissue for hyperinsulinism. The steps in the technic of such resections employed in the patients reported here may be summarized as follows (Fig. 1):

Anesthesia: Preferably continuous spinal.

1. High midline, transverse or inverted-T incision.

2. Approach to the pancreas by transection of the gastrocolic omentum from the level of the head of the pancreas to the gastrosplenic vessels.

3. Retraction of stomach upward and transverse colon downward.

* Read before The American Surgical Association, May 3–4, 1944, Chicago, Ill.

4. At this point, the body of the pancreas may be excised in one of three ways, depending upon the expediency of each situation.

a. Transection of pancreas at level of the neck, with resection proceeding distally of body and tail; hemostasis being secured by ligation of branches from the splenic vessels.

b. Division and ligation of gastrosplenic vessels, then transection of neck of pancreas and splenic artery and vein at this level, with excision of body of pancreas and spleen *en masse* proceeding from the neck distally.

c. Division and ligation of gastrosplenic vessels, then elevation of spleen by grasping in right hand; this brings the tail and body of pancreas forward together with splenic artery and vein. Transection of neck of pancreas and splenic vessels at level of superior mesenteric vessels, with excision of body of pancreas and spleen *en masse*.

5. Interrupted interlocking silk mattress sutures are placed about 0.5 cm. proximal to the cut edge of the remaining neck of pancreas. The transected main pancreatic duct, if apparent, is grasped with a hemostat and ligated separately.

6. The transverse mesocolon is repaired except in the region below the pylorus. Here, one or two soft rubber drains are inserted to the site of pancreatic transection.

7. Closure of the abdominal wound.

In some instances of redundant stomach the gastrohepatic omentum may be transected, the stomach retracted downward and the body of the pancreas excised over the lesser curvature of the stomach.

Total duodenopancreatectomy and splenectomy for practically complete replacement of the pancreas by carcinoma was performed in two patients as follows:

1. In each instance the pancreas was exposed *via* the gastrocolic route. 2. The gastrosplenic vessels were divided. 3. The spleen was grasped with the right hand and elevated to mobilize the body of the pancreas. 4. The splenic vessels were divided about three centimeters distal to the origin of the portal vein. 5. The peritoneum along the convex border of the duodenum was incised to mobilize the head of the pancreas and duodenum. 6. The pylorus was transected several centimeters proximal to the pyloric sphincter, and upper segment of stomach closed. 7. The common bile duct was transected below the level of the superior border of first portion of duodenum. 8. The head of the pancreas and duodenum were completely mobilized and lifted away from the superior mesenteric vessels, the uncinate process of the pancreas and terminal portions of duodenum brought out to the right from beneath these vessels after transection of the ligament of Treitz. 9. Transection of jejunum just distal to ligament of Treitz and closure of distal segment. 10. Removal of entire pancreas and duodenum with attached lower pylorus and spleen. 11. Gastro-enterostomy (Billroth II). 12. Choledochojejunostomy using loop of jejunum about 15 cm. distal to above anastomosis; jejunojejunostomy between loops to choledochojejunostomy.

CASE REPORTS

RESECTIONS OF THE BODY OF THE PANCREAS AND SPLEEN

Case 1.—J. L. (233821), male, age 32. (Previously reported in detail). The patient had attacks of hyperinsulinism and was explored in another institution in September, 1939, where two tumors in the tail of the pancreas were observed and biopsied, with diagnosis of islet-cell carcinoma. In January, 1940, a large rounded tumor, 15 cm. in greatest diameter, was resected together with portions of infiltrated stomach wall and jejunum. There was no evidence of metastasis. He was free from attacks of hyperinsulinism until July, 1942, when these recurred, and in August, 1942, exploratory

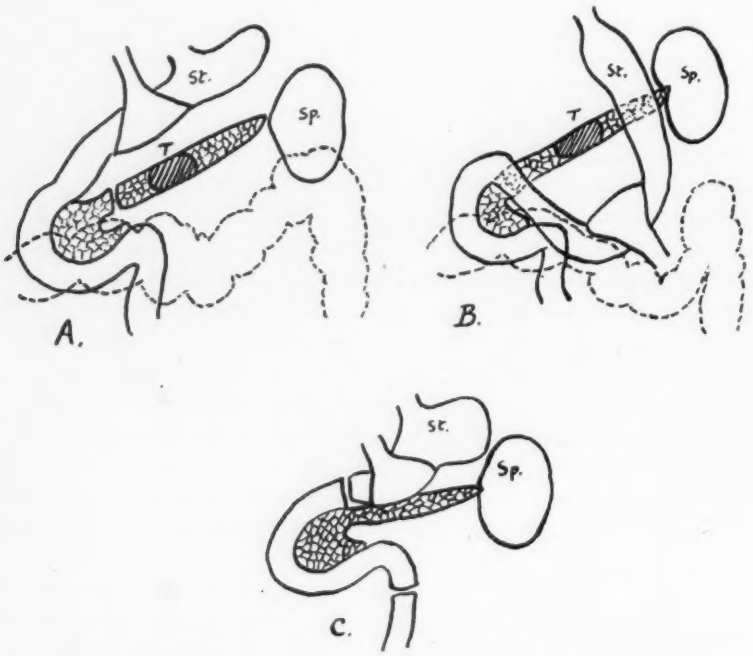

FIG. 1.—A. Schematic representation of excision of body of pancreas and spleen *via* gastrocolic route. St. stomach. Sp. spleen. T. neoplasm in body of pancreas.
B. Showing access to body of pancreas by downward retraction of redundant stomach.
C. Total pancreatectomy with total duodenectomy and splenectomy. This is followed by gastrojejunostomy and choledochojejunostomy.

celiotomy revealed multiple hepatic metastases—biopsy only was performed. Attacks recurred after a short respite, and from June to December, 1943, alloxan was injected in attempted chemotherapy.[8] The attacks were controlled for periods of three weeks. Finally, at the patient's request another celiotomy was performed to remove the remaining head of the pancreas and what liver metastases could be resected. The portal vein was divided accidentally, necessitating ligation. He died two hours after operation. He survived three years and 11 months after excision of the primary growth.

Case 2.—P. F. (162585), female, age 73, was admitted, July 27, 1940, complaining of a mass in the epigastrium and dull intermittent epigastric pain, both noted for two months. She stated that she had had "stomach trouble for 50 years." Examination revealed a firm, rounded mass in the midepigastrium situated over the aorta and transmitting a bruit. Roentgenograms of the stomach were normal. The clinical impression was abdominal tumor of undetermined origin or aortic aneurysm. Celiotomy was per-

formed August 1, 1940. The mass was discovered to be a rounded carcinoma in the body of the pancreas, 4 cm. in diameter, near the neck. The neck was transected and body of pancreas, with spleen, resected. There were a few metastatic nodes in the liver, not exceeding 1 cm. in diameter, and several enlarged and firm periaortic lymph nodes. Immediate recovery from the operation was satisfactory, but the patient expired suddenly on the third day. Necropsy revealed an antemortem thrombus in a branch of the portal vein and several hepatic infarcts. There were several old healed myocardial infarcts.

Case 3.—M. K. (295967), male, age 66. A physician, in June, 1942, developed constant severe epigastric pain not related to eating or bowel movements. Appetite became very poor, and he lost 12 pounds in five months. The pain finally developed a high girdle distribution, was very severe, especially upon lying down, and became more or less

FIG. 2.—Case 3: Surgical specimen consisting of entire body of pancreas infiltrated by carcinoma, and spleen.

constant. After numerous consultations, he made his own diagnosis of neoplasm of the pancreas. Icterus had developed. Physical examination was negative except for upper abdominal tenderness. Celiotomy was performed November 2, 1942, and revealed a carcinomatous mass in the midportion of the body of the pancreas, with multiple hepatic and peritoneal metastases. With the abdomen open it was decided to resect the body and tail of the pancreas in an attempt to alleviate pain. The jaundice appeared to be due to intrahepatic obstruction from metastases as the common duct was not enlarged. The surgical specimen is shown in Figure 2. Immediate recovery was satisfactory and there was much less pain during the postoperative period. He died five weeks later, cachexia having become very pronounced. Necropsy revealed carcinomatosis.

Case 4.—H. D. (170446), female, age 55, was admitted September 5, 1943, complaining of generalized fatigue for over a year; periods of nausea and vomiting for one month; and loss of 20 pounds during the past four months, attributed to "dieting." Slight icterus. On physical examination, the right lobe of the liver was moderately enlarged but smooth. Roentgenologic examination revealed normal stomach, extrinsic pressure narrowing in the upper half of the descending portion of the duodenum and nonvisualization of the gallbladder. The clinical impression was carcinoma of the head of the pancreas. Celiotomy was performed September 11, 1943. An oval carcinomatous mass, about 4 cm. in diameter, was found in the proximal portion of the body of the pancreas and extending into the neck. It was planned to excise this by pancreatoduodenectomy,

with transection of the pancreas in midportion of the body well beyond the neck. The operation was begun in the usual manner by mobilizing the head of the pancreas and duodenum. When mobilization of the neck was attempted the first portion of portal vein was accidentally opened due to tumor infiltration of an appreciable segment of the wall. Before hemorrhage could be arrested the portal and superior mesenteric veins had been ligated and had retracted some distance from each other. It was felt that the patient would not survive and that termination of the operation as quickly as possible was indicated. Transection of the pancreas through the tumor was carried out to excise

FIG. 3.—Case 4: Necropsy specimen obtained on tenth postoperative day. L. liver and gallbladder. P. ligated portal vein; O. proximal portion of body of pancreas, with bisected portion of tumor; T. *in situ;* small white arrow to right of pancreas indicates site of ligation of superior mesenteric vein.

the mobilized lower stomach, head of pancreas and duodenum. A gastrojejunostomy was performed and a urethral catheter tied into the transected common duct and brought to the outside through the abdominal wound. The immediate postoperative course was astounding in that recovery was relatively satisfactory. She survived for ten days. Necropsy revealed acute biliary fibrinopurulent peritonitis. She had had a pelvic operation 20 years previously. There were extensive omental adhesions to the lower anterior abdominal wall and in addition to this collateral venous circulation was obvious at the base of the mesentery of the small bowel and in the retroperitoneal spaces. The necropsy specimen showing ligated portal and superior mesenteric veins is demonstrated in Figure 3.

Case 5.—G. M. (50813), male, age 49, was admitted October 9, 1943, complaining of severe spasms of pain in the back of five months duration, with radiation to each side which was described as affording the sensation of "giant ice tongs" having been applied to his body. There had been loss of 20 pounds weight in four months. Palpation of the abdomen was negative except for moderately enlarged liver. Roentgenologic study of the alimentary tract was negative. The patient had been luetic but had had extensive treatment. The clinical impression was carcinoma of the pancreas. Celiotomy was performed October 11, 1943. A tumor mass, 10 cm. in length and 6 cm. in width, was situated along the superior border of the pancreas and apparently arising from this organ. No metastases were apparent. Resection of the body of the pancreas and spleen together with adherent left adrenal gland was carried out (Fig. 4). There was diffuse but not marked cirrhosis of the liver and this organ was biopsied. Immediate convalescence was satisfactory. Pain was completely relieved. He was discharged on the 20th day. At home,

he did not continue to improve, icterus developed and became progressively worse. Weakness became more pronounced and there was loss of appetite. He succumbed November 18, 1943, five and one-half weeks after operation. Necropsy revealed large intrahepatic metastases not appreciable on the surface, situated just within the porta hepatis and occluding the right and left hepatic ducts.

Case 6.—C. P. (325186), female, age 55, was admitted, January 12, 1944, complaining of "gas pains" in the left upper quadrant and pain in the region of the umbilicus, with radiation through the body to the back, two months duration. She stated she had had "stomach trouble all of her life." There was loss of 20 pounds weight in the past

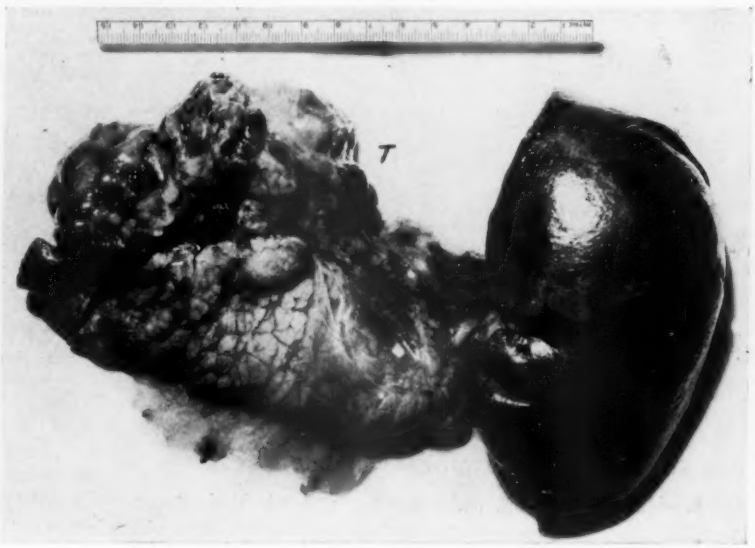

FIG. 4.—Case 5: Surgical specimen consisting of entire body of pancreas with large carcinoma (T) arising from upper border, and spleen.

month. Physical examination revealed marked tenderness in the upper abdomen and a firm tender nodule within the umbilicus, suspected of being a metastasis. Cholecystograms revealed nonvisualization of the gallbladder. The clinical impression was possibly carcinoma of the gallbladder. Celiotomy was performed on January 15. The lower portion of the stomach was studded with metastatic nodules as was the falciform ligament and deeper aspect of the umbilicus. In the wall of the lesser curvature of the stomach there was an oval, firm area assumed to be malignant neoplasm. In the distal portion of the body of the pancreas there was an oval, firm mass, 4 cm. in greatest diameter, obviously carcinoma. The liver and peritoneal surfaces were free from metastases. The gallbladder wall was slightly thickened and it contained numerous small stones. A subtotal gastrectomy was performed leaving about one-sixth of the stomach. The spleen was then mobilized and used as a handle to elevate the body of the pancreas. The latter was transected about 3 cm. distal to the neck, with resection of tumor-bearing portion of pancreas and the spleen. The stump of pancreas was closed with interrupted interlocking silk mattress sutures. A Pólya gastrojejunostomy was performed. The falciform ligament and umbilicus with surrounding tissue were excised (Fig. 5). The gallbladder filled with small stones was not removed. Convalescence was rather stormy due primarily to failure of function of the gastro-enterostomy. The patient however was sustained by glucose, casein digest, and gelatin intravenously, and eventually improved. She was dis-

charged on the 44th day after operation, able to partake of general diet, free from pain, and in fair general condition. Three months after operation her condition remains relatively satisfactory. There is no abdominal pain, she is able to eat a varied diet and is ambulatory.

FIG. 5.—Case 6: Surgical specimen consisting of: Pt. distal portion of body of pancreas with carcinoma (C) and spleen.
S, lower 5/6 of stomach resected because of serosal metastases from pancreatic neoplasm. G. large metastasis which at operation was thought to be primary carcinoma in stomach. U. umbilicus and falciform ligament containing metastases.

TOTAL PANCREATECTOMY

Case 7.—H. H. (302199), male, age 67, was admitted, February 24, 1943, complaining of loss of 40 pounds weight, diarrhea, continuous upper abdominal pain of five months duration, icterus for two months, with severe pruritis, and pain in the chest, cough, edema of ankles, and hoarseness of two weeks duration. Physical examination revealed dullness and absent breath sounds in the left thorax; the abdomen was negative except for a moderately enlarged and smooth liver and questionable fluid wave. Icteric index 115. Roentgenograms of the chest showed massive left hydrothorax. The stomach and colon were normal. Left thoracentesis was performed (625 cc. of bloody fluid), on February 22. Celiotomy was performed February 26, 1943. The entire pancreas was found extensively indurated by carcinoma; there were several hepatic metastases. Total pancreatectomy, total duodenectomy and splenectomy with gastrojejunostomy and choledochojejunostomy were performed. Immediate recovery was satisfactory but the patient succumbed on the third day. Necropsy revealed massive bilateral pulmonary consolidation as the immediate cause of death.

Case 8.—N. R. (309791), male, age 29, was admitted, May 20, 1943, because of 40 pounds weight loss in four months, upper abdominal pain, more or less constant, and increasing in severity, three months; increasing icterus and pruritus, two months. Physical examination was essentially negative except for upper abdominal tenderness, moderate enlargement of the liver and severe icterus (icteric index 159). Celiotomy was performed May 27, 1943. The pancreas was diffusely involved by carcinoma; there were no hepatic metastases. Total pancreatectomy, with total duodenectomy and splenectomy, gastrojejunostomy and choledochojejunostomy were performed. Immediate recovery was satisfactory, but after the second day the course was rather stormy. Less insulin than anticipated was required. The details of the postoperative course from this standpoint will be reported elsewhere (Goldner and Clark). He succumbed on the ninth

day. Necropsy revealed metastases to mediastinal lymph nodes, suprarenals, both kidneys, a small perforation of the common duct from which there was a sinus to the abdominal wound; bilateral partial atelectasis, in short, the patient died of exhaustion.

A summary of the results in the above series of patients is given in Table I:

TABLE I

RESECTIONS OF THE BODY OF THE PANCREAS AND SPLEEN

Case No.	Pathologic Condition	Course
Case 1	Islet-cell carcinoma invading entire body.	Lived 3 years, 11 months. Died after 3rd celiotomy as a result of portal vein ligation.
Case 2	Carcinoma, proximal portion of body. Few hepatic metastases.	Died 3rd day (portal thrombosis?)
Case 3	Carcinoma invading entire body. Multiple hepatic metastases.	Lived 5 weeks. Died of carcinomatosis.
Case 4	Carcinoma of proximal portion of body and neck.	Lived 9 days. Died of bile peritonitis. Portal vein ligated.
Case 5	Carcinoma arising in upper border of body.	Lived 5.5 weeks. Died of "exhaustion." Necropsy revealed single large intrahepatic metastasis.
Case 6	Carcinoma of tail of pancreas, with metastasis to stomach and retroperitoneal lymph nodes.	Living 3 months after resection of body of pancreas and radical gastrectomy. Evidence of recurrence.
	TOTAL PANCREATECTOMY AND DUODENECTOMY WITH SPLENECTOMY	
Case 7	Entire pancreas replaced by carcinoma. Metastases in liver.	Died 3rd day. Massive bilateral lobar pneumonia.
Case 8	Entire pancreas replaced by carcinoma. Metastases in liver.	Died 9th day of "exhaustion."

Immediate operative mortality, 50% (4 cases).

Survivals, 4 cases; 5 weeks, 5.5 weeks, 3 years, 11 months, one living 3 months in fair condition, respectively.

SECONDARY INVOLVEMENT OF BODY OF PANCREAS

Neoplasms arising in viscera adjacent to the body of the pancreas may involve the latter by direct extension. This does not constitute a contraindication for excision of these growths since resection of the body and tail of the pancreas *en masse* with them is quite feasible. The author has performed total gastrectomy, with splenectomy, transverse colectomy, and resection of the body and tail of the pancreas for carcinoma primary in the stomach. The patient survived six months, with a period of symptomatic improvement. In another patient a large adrenal (left) carcinoma, 20 cm. in diameter, infiltrating the under surface of the left diaphragm, the muscles of the left posterior abdominal cavity, the hilum of the spleen, about the upper pole of the left kidney, and the posterior surface of the body and tail of the pancreas, was resected *en masse,* with its extensions, including the under surface of diaphragm, body and tail of pancreas, *etc.* The patient is living and well, without evidence of recurrences two years later. He is at work full time as a draughtsman. A third patient with a very large carcinoma of the splenic flexure infiltrating the stomach, hilum of the spleen, and body of the pancreas was recently subjected to successful resection of the lower three-fourths of the stomach, together with body of the pancreas, spleen, most of transverse colon, and upper two-thirds of descending colon. Other cases of excision of portions of the body of pancreas with neoplasms arising in adjacent organs have been reported elsewhere.[9] The success of massive resections as described above is dependent, to a large extent, upon the liberal use of blood transfusions. Transfusions are begun at the out-

set of the operation and continued as needed to maintain a systolic pressure of 100 Mm. of mercury. Quantities of 2000 to 3000 cc. are sometimes necessary and must be employed without hesitation. Plasma transfusions alone do not suffice.

FIG. 6.—Case 8: Surgical specimen consisting of entire pancreas infiltrated by carcinoma, spleen, lower stomach and entire duodenum. Arrow indicates duodenojejunal junction.

DISCUSSION.—In six of the eight patients subjected to partial or total pancreatectomy, metastases were apparent at the time of operation. What, then, was the justification for the operation? With the abdomen open it was felt that the primary growth should be resected as a means of palliation since in all of these patients (except Case 1) constant severe pain was an outstanding complaint. The pain of cancer of the body of the pancreas is characteristically severe, non-colicky, and more or less constant, and its amelioration would constitute a degree of palliation. Appreciable amelioration of pain was actually accomplished in Cases 3, 5 and 6. However, the question remains, principally of academic interest, whether such relief was afforded by the removal of the cancerous pancreas, or by the extensive division of sympathetic nerves which such operations entail.

The results obtained in the above series of patients are far from encouraging. The great difficulty in this field lies in the fact that patients are not subjected to celiotomy early enough in the course of the disease to permit of complete excision by radical resections. Cancer of the body of the pancreas is, indeed, a silent lesion in its earlier development (except when it may arise in the neck and proximal portion of the body and produce icterus, as in Case 4). It is removed from the alimentary and biliary tracts and, therefore, does not produce obstructive symptoms early. With exception of Case 1 (insulin-pro-

ducing islet-cell carcinoma) the above patients' serious complaints were of two, five, four, five, two, five, and four months duration, respectively, an average of three and eight-tenths months. Early in these periods it would appear to have been hardly justifiable from the histories as given, to make the diagnosis of carcinoma of the body of the pancreas and advise operation. There is no purpose to be served by repeating here the classical signs and symptoms of carcinoma of the body of the pancreas, since these are well known and when present the patients usually are in an advanced stage of the disease. As mentioned in a previous communication, there is perhaps some parallelism between the present situation surrounding the surgery of cancer of the pancreas and the situation of gastrectomy for carcinoma of the stomach during the quarter century following Billroth's first successful pylorectomy. Relatively few patients were subjected to partial gastrectomy during this period and the large majority of the patients who underwent exploratory celiotomy for gastric cancer were considered inoperable. Indeed, the future of gastrectomy for cancer was not considered very bright by some authorities of that period. It is hoped that, with the feasibility of radical pancreatectomy now well established, persistent efforts will result in a more hopeful future for this particular branch of surgery than would appear to be justifiable on the basis of experiences up to the present time.

SUMMARY

Cancer of the body of the pancreas is manifested clinically late in the course of the disease. While radical resection of such neoplasms is feasible, few patients are subjected to operation early in the evolution of these growths.

Six instances of resection of the body of the pancreas with splenectomy and two instances of total pancreatectomy, with total duodenectomy and splenectomy, are recorded. The immediate operative mortality was 50 per cent (four cases, including the two total pancreatectomies). One patient with islet-cell carcinoma invading the entire body and later manifesting hepatic metastases lived three years and 11 months. Of the remaining three, two survived five weeks and five and one-half weeks, respectively, had metastases at the time of operation, but experienced appreciable amlioration of severe abdominal pain. The third is living, comfortable, and in fair general condition three months following resection of the body for carcinoma and subtotal gastrectomy for metastases to the stomach. Metastases to the falciform ligament and umbilicus were also resected.

REFERENCES

[1] Oberling, C., and Guerin: Cancer of the Pancreas. Collection of H. Hartman and L. Berard, Paris, France, 1930. Gaston Dorin & Cie.

[2] Gordon-Taylor, G.: The Radical Surgery of Cancer of the Pancreas. ANNALS OF SURGERY, 100, 206–214, 1934.

[3] Doberer, J.: Contributions to Pancreatic Surgery. J. Internat. de Chir., 3, 357–377, 1938.

[4] Milhet, H., *et al.*: Large Carcinoma of the Pancreas Treated by Subtotal Pancreatectomy. Mem. Acad. de Chir., 66, 5–13, 1940.

[5] Harvey, S., and Oughterson, A.: The Surgery of Carcinoma of the Pancreas and Ampullary Region. Trans. Am. Surg. Assn., 60, 1066–1090, 1942.
[6] Rockey, E. W.: Total Pancreatectomy for Carcinoma. Trans. Am. Surg. Assn., 61, 603–611, 1943.
[7] Brunschwig, A.: Surgery of Pancreatic Tumors. C. V. Mosby Co., St. Louis, Mo., 1942.
[8] Brunschwig, A., *et al.*: Alloxan in the Treatment of Insulin-producing Islet-cell Carcinoma of the Pancreas. J.A.M.A., 124, 212–216, 1944.
[9] Brunschwig, A.: Extending Surgical Treatment of Carcinoma of the Colon. Surg. Clinics, N. America, Saunders and Co., Philadelphia, Pa., February, 1944.

DISCUSSION.—DR. ROY D. MCCLURE, Detroit, Mich.: I wish to report a successful case of total pancreatectomy for primary carcinoma of the pancreas, showing the feasibility of Doctor Brunschwig's experience:

A 46-year-old male was admitted to the Henry Ford Hospital, January 2, 1944, for treatment of painless obstructive jaundice. A diagnosis of probable carcinoma of the pancreas was made on the basis of the history of gradually deepening jaundice, plus the presence of a palpable mass in the midepigastrium in the region of the pancreas.

Celiotomy by my associate, Dr. Lawrence Fallis, was performed, January 14, 1944, under nupercaine anesthesia. A transverse incision was made in the transpyloric plane. Exploration revealed a distended gallbladder, a dilated common duct, and an enlarged pancreas which was indurated throughout.

A one-stage, complete pancreatectomy, duodenectomy and splenectomy was performed. Section showed carcinoma of the pancreas. Restoration of the continuity of the intestinal tract was by terminolateral gastrojejunostomy, with implantation of the common duct into the jejunum proximal to the anastomosis.

The patient left the hospital on the 23rd day after operation, following an uneventful postoperative course. He returned to part-time work two months later. His insulin requirements have been 26 units of protamine insulin daily, supplemented about twice weekly by 8 units of regular insulin.

This patient was shown in our clinic one week ago today. His jaundice has entirely disappeared. His strength is improving, and he has the appearance and mental attitude of a healthy normal man. Doctor Fallis is continuing his studies of this case. Not so many years ago we thought the pancreas an essential organ.

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